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Учреждение образования  
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии  
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Протокол №7 от 30.08.2017

**МЕТОДИЧЕСКАЯ РАЗРАБОТКА**  
Для проведения занятия со студентами  
3 курса ФПСЗС, обучающихся на английском языке  
по патологической физиологии

Тема: **Патология тканевого роста. Опухоли**

Theme: **Pathology of tissue growth. Tumors**

Время 3 ак. часа

**Actuality of the theme.** By the prognoses of Worldwide health protection organization morbidity and death rate from oncologic diseases in the whole world will grow in 2 times for period from 1999 year for 2020: from 10 to the 20 million new cases and from 6 to the 12 million registered deaths.

Taking into account that in the developed countries there is a tendency to deceleration of growth of morbidity and death rate from malignant tumors (due to the prophylaxis and due to the improvement of early diagnostics and treatment), clearly, that a basic increase will be at developing countries (countries of former USSR). That is why doctors have to expect serious increase of morbidity and death rate from oncopathology. From data of Committee of cancer prophylaxis 90% tumors are related to influencing of external factors, and 10% - depend on genetic factors.

That is why it is necessary for future specialist to know etiological factors and « risk factors» of tumors origin. Taking into account that tumors appear at the different age, race, sex people understanding of carcinogenesis and metastasis mechanisms and differences of innocent tumors from malignant are necessary for the doctor of any profession.

**Learning goals of the lesson:** to study etiology and pathogenesis of tissue growth disorders.

**Educational goals of the lesson:** formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

**Objectives of the lesson:**

1. To know causes and mechanisms of onset and development of a tumor, characteristics of tumor cells.
2. To be able to explain relationship tumor and body.
3. To know basic tumor markers.

**To repeat the following questions from related disciplines to ensure absolute mastery of the material:**

1. Structure of cell (histology, cytology, embryology disciplines).
2. Cell populations and cycle landmarks; mechanisms of cell division (medical biology and genetics discipline).

**Control questions of the lesson:**

1. Tumor: definition, types, etiology.
2. Biological features of tumor growth.
3. Metastasis: definition, stages, mechanisms. Recurrence of tumors.
4. Malignant and benign tumors, features of their growth.
5. Theories of tumor pathogenesis.
6. Antineoplastic resistance of body.
7. Systemic manifestations of tumor disease.
8. Principles of prevention and therapy of tumors.

**Calculation of study time**

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

## Additional materials:

### Typical forms of abnormal tissue growth:

- Pathologic hypertrophy and hyperplasia
- Pathologic hypotrophy and atrophy
- Metaplasia
- Dysplasia
- Benign tumor
- Malignant tumor

**Cellular atrophy** decreases the cell substance and results in cell shrinkage. The size of all the structural components of the cell usually decreases as the cell atrophies. Causes of atrophy include disuse, denervation, lack of endocrine stimulation, decreased nutrition, or ischemia. Disuse atrophy is seen in muscles that are not used. Denervation atrophy occurs in the muscles of paralyzed limbs. Lack of endocrine stimulation causes changes that may occur in reproductive structures during menopause. During prolonged periods of malnutrition, the body may undergo a generalized wasting of tissue mass. Ischemia reduces blood flow and delivery of oxygen and nutrients to tissues.

**Hypertrophy** increases the amount of functioning mass by increasing cell size. This allows the cell to achieve an equilibrium between demand and function. Hypertrophy usually is seen in cardiac and skeletal muscle tissue. These tissues cannot adapt to increased workload by mitosis to form more cells. The increase in cell components is related to limitations in blood flow. Hypertrophy may be either physiologic or pathologic. In myocardial hypertrophy, initial enlargement is caused by dilation of the cardiac chambers in response to valvular disease or hypertension. This adaptation is short-lived and is followed by increased synthesis of cardiac muscle proteins that allows cardiac muscle fibers to do more work. Ultimately, advanced hypertrophy becomes pathologic and can lead to heart failure.

**Hyperplasia** is an increase in the number of cells of a tissue or organ. It occurs in tissues where cells are capable of mitotic division. Hyperplasia is a controlled response to an appropriate stimulus and ceases once the stimulus has been removed. Breast and uterine enlargement during pregnancy are examples of a physiologic hyperplasia that is hormonally regulated. A pathologic hyperplasia occurs when the endometrium enlarges because of excessive estrogen production. Then, the abnormally thickened uterine layer may bleed excessively and frequently. Compensatory hyperplasia enables certain organs, like the liver, to regenerate after loss of substance.

**Dysplasia** is deranged cell growth that results in cells that vary in size, shape, and appearance of mature cells and is related to hyperplasia. Minor degrees of dysplasia occur in association with chronic irritation or inflammation in the uterine cervix, oral cavity, gallbladder, and respiratory passages. Dysplasia is potentially reversible once the irritating cause has been removed. Dysplastic changes may progress to neoplastic disease. This makes dysplasia a phenomenon of importance.

**Metaplasia** is a reversible conversion from one adult cell type to another adult cell type. It allows for replacement with cells that are better able to tolerate environmental stresses. In metaplasia, one type of cell may be converted to another type of cell within its tissue class (i. e., an epithelial cell cannot change to a connective tissue cell). An example of metaplasia is the substitution of stratified squamous epithelial cells for ciliated columnar epithelial cells in the airways of the person who is a habitual cigarette smoker.

**Tumor** — is a typical pathological process characterized by irregular limitless growth of cells with different degree of differentiation.

Etiological factors, which cause malignant tumors, are called **cancerogens**.

Agents, intensifying an effect of carcinogens, but not causing tumors themselves are called **cocancerogens**.

**Carcinogens**, which have these effects in combination, are called **syncancerogens**.

**Proto – oncogene** is a gene of normal genome, it takes part in the cells proliferation control. As a result of somatic mutations proto – oncogene can change into oncogene

**Oncogene** is a protein providing proliferation and differentiation of cells (nuclear proteins and growth factors). They may provoke malignant growth in case of the oncogenes mutation or activation by retroviruses.

**Oncosuppressors** (antioncogenes) are able to inhibit proliferation of the transformed cells.

### **Theory of carcinogenesis:**

1. **Mutation Theory** (G.Boveri), according to which the basis for the transformation of a normal cell into a tumor cell is a mutation.
2. **Epigenomic theory** (K.Geydelberg et al.). According to this theory, the transformation of normal cells due coexist repression of genes that inhibit cell division, and derepression of genes that stimulate their division. This leads to uncontrolled cell division and transfer their epigenomic changes inherited.
3. **Viral - genetic theory** (L.A.Zilber et al.), According to which the malignant transformation associated with the introduction of the cellular genome of the viral DNA (or DNA copies of viral RNA).
4. The theory of endogenous viruses (R. Huebner, G. Todaro). According to this theory, the viral genes or oncogenes, are in the cellular genome of humans and animals in the repressed state throughout the life of the organism and are inherited as normal cellular genes. Viral oncogenes can be activated by exposure to any carcinogen, resulting in the conversion can be a normal cell into a tumor cell.
5. Theory formation of oncogenic genes - protoviruses (N.Temin, D.Baltimore). According to this hypothesis, under normal conditions at normal RNA matrix using reverse transcriptase are synthesized cellular DNA copies required to strengthen the function of normal genes. Exposure to carcinogens results in the disruption and structural changes RNA matrix, which leads to the synthesis of the mutation of DNA copies. These mutant DNA copies in potency may become matrix for formation of endogenous RNA virus, the latter incorporated into the cellular genome and cause malignant transformation of cells.
6. **Theory of DNA repair deficiency** (M.M.Vilenchik). According to this theory, the cell DNA even in normal conditions, is constantly exposed to aggressive influences by exogenous and endogenous mutagens, including oncogenic genes. In most cases, while the tumor cell transformation does not occur because of the function of DNA repair systems that remove damaged areas of nucleotides. Factors that reduce the activity of DNA repair system, facilitate the development of spontaneous or induced mutations, including and tumor that facilitates malignant transformation of cells.
7. **Theory deficiency of immune surveillance** of the normal antigenic structure the internal environment (F.Bernet). According to this theory in the body constantly occurring, spontaneous mutations, resulting formed mutant cells, including tumor comprising in its composition antigens bearing the signs of foreign genetic information. Cells with such antigens are subject to destruction by effector mechanisms of the immune system. Under conditions of immunosuppression such spontaneously arising tumor cells not exposed to destruction and continue to proliferate to form a tumor.
8. Two-stage theory of carcinogenesis (I.Berenblum). According to this theory distinguish two stages:
  - induction (initiation), - a condition most likely due to a mutation of one of the genes regulating cell proliferation that leads to the formation of a latent, the sleeping tumor cells.
  - Promotion - activation and proliferation of previously latent tumor cells with outcome in tumor formation. Ie the impact of additional factors-promoter induces tumor cells to divide, resulting in generated a critical mass of initiated cells.
9. **Theory oncogenes of viral and other nature** (D.Baltimore, M.Bardatsid). Currently about 30 of oncogenes detected in 20 oncornaviruses studied. It was established that the DNA of somatic mammalian cell contains regions homologous in nucleotide composition sarcoma virus oncogene Rausa- src (proto-oncogene). In normal cells, analogue of viral oncogene inactive. The sources of cellular oncogenes are cellular protooncogenes. When changing the their structure or activity under the influence of carcinogens they become active cellular oncogenes that cause malignant transformation of cells.

### **Stage of carcinogenesis**

1. Initiation
2. Promotion
3. Progression
4. Outcomes

## Tumor etiology

- chemical
- physical
- biological
- poly etiologic theory.

## Chemical carcinogenes

### Classification of chemical carcinogens:

- I. By nature:
  - exogenous
  - endogenous
- II. By chemical structure  
**Endogenous:**
  - a) polycyclic aromatic hydrocarbons (methylcholantren), which are synthesized from a cholesterol, bilious acids and steroid hormones
  - b) metabolites of amino acid (tryptophan) exchanges;
  - c) due to exceed secretion of tropic hormones by anterior pituitary**Exogenous:**
  - a) polycyclic aromatic hydrocarbons: 3,4-benzpyrene, dimethylbenzantracene;
  - b) aromatic amines with benzene rings and amine groups in the structure (aniline and his derivates);
  - c) nitro compounds (nitrosamine, predecessors (nitrite, amino acid, amidopyrine) in presence of hydrochloric acid;
  - d) mycotoxins (aflatoxin produced by *Aspergillus flavum*);
  - e) heterocyclic hydrocarbons;
  - f) simple inorganic connections: arsenic and his connections, salts to the beryllium, chrome, nickel, cobalt (may cause tumors of bone).
- III. By origin:
  - Natural
  - artificial
- IV. By mechanism of the carcinogenic influencing divided on:
  - direct action
  - indirect action.

## Pathogenesis of chemical carcinogenesis

### 1. Initiation

Action of chemical carcinogen led to transformation of cell from *normal* to *atypical* (tumor).

The followings molecular changes are possible:

- Point mutations of proto-oncogene;
- mutations of antioncogene, which regulate expression of proto-oncogenes;
- chromosomal aberration;
- formation of imperfect viruses is with oncogenic properties;
- oppression (syn: inhibition) of the system of natural and specific antitumoral (anticancer) resistance, in particular, development of ID state.

### 2. Promotion

During the stage of promotion the transformed cell gets a stimulus to the division, a tumor begins to grow. Matters which stimulate the division of the transformed cells got the name of promoters. Strong promoters are ethers which activate protein kinase C, which regulates a cellular division. It is necessary to notice, that most studied chemical carcinogens have property as initiators, so and promoters. Between initiation and promotion can pass much time (sometimes years).

### 3. Progression — is high-quality changes of properties of tumor in the process of its development. In this period a tumor acquires all more and more malignant properties.

The cells of tumors differ high changeability, their population is heterogeneous. There is a permanent fight of cells for a survival in the unfavorable terms of existence (deficit of substratum, oxygen

and etc). There are tumors in which on 100 again well-educated cells there are 80-90 lost. It is basis of their natural selection - those cells which are most adjusted to existence in such terms survive only. And most adjusted it is most simple the cells of tumors, which lost it functions are specialized and saved property of boundless division only. That is why, main direction of tumor progression are subsequent (following) malignization of tumors.

#### 4. Outcomes

#### Physical carcinogenes

1. ionizing radiation
2. ultraviolet radiation
3. mechanical influencing (the protracted pressure on tissues)
4. high temperature.

#### 1. Initiation

**Ionizing Radiation.** Particulate radiation ionizes the water in affected cells. This results in the formation of radicals and peroxides that lead to fracture and cross-linkage of DNA strands. Point mutations occur where DNA repair is unsuccessful. Uncontrolled proliferation occurs where this mutation affects a proto-onc.

**Ultraviolet radiation** Sunlight contains ultraviolet B radiation, which only penetrates superficially. This causes formation of DNA thymine dimers in the basal epidermis. Point mutations occur in a proto-onc where DNA repair is unsuccessful. This results in uncontrolled proliferation.

#### **Mechanical influencing (Foreign Bodies)**

**Asbestos:** Inhalation of asbestos dust leads to chronic inflammation, mesothelioma, and lung cancer.

**Bivalent metals** such as nickel cause mutation of the p53 suppressor gene, leading to malignant connective tissue tumors (sarcomas).

**Schistosoma haematobium:** Infestation leads to chronic inflammation of the bladder (urocystitis). The resulting chronic tissue repair stimulus leads to carcinoma of the bladder.

2. Promotion
3. Progression
4. Outcomes

A *mechanism* of carcinogenic action of physical factors is the same, as well as at the action of chemical carcinogens.

#### Biological carcinogenesis.

#### **DNA genome viruses:**

- Papova viruses
- Adenoviridae
- Herpetoviridae
- Hepadnoviridae
- Poxviridae

#### **RNA genome viruses:**

- Oncoviridae
- Spumaviridae
- Lentiviridae
- Virus of T-cellular lymphoma

#### **Stages of viral oncogenesis:**

#### 1. Initiation

1) **reception of virus** is co-operating of virus **with** the certain structures of plasmatic membrane of cell (by receptors). Absence of the proper receptors is explain specific immunity to the viral infection.

2) **Internalization** is undressing and penetration of **virus in a cell.**

3) **Integration** (association) of viral genome into the genome of cell. It is the central and obligatory stage of viral oncogenesis.

4) **Persistence** (permanent stay) of virus in the genome of cell. Thus a virus propagates oneself together with a cell. Such viral infection is named *abortive*. *Abortive course* is the necessary condition of transformation of normal cell in a tumor under act of virus.

5) **Transformation of cell:**

a) *epigenomic* is caused viruses which contain oncogenes, which violate adjusting of cellular division and thus cause transformation of cell:

b) *mutational*, when oncoviruses does not contain oncogenes, but able to cause the mutation (transformation) of cellular proto-oncogene in oncogene, which predetermines suppression gene-repressor and expression (activating) of gene-initiator of the transformed fission.

2. **Promotion** is a stimulus of tumor to growth.

3. **Progression** is acquisition by the tumor of new (more malignant) qualities.

4. **Outcomes**

### **Tumor Dissemination**

A benign tumor remains within its tissue of origin and cannot extend across long distances into other organs. In contrast, the spread of malignant tumors exhibits the following four characteristics:

- **Infiltration:** The tumor cells penetrate the surrounding tissue.
- **Invasion:** The tumor cells penetrate lymph and blood vessels.
- **Tissue destruction** occurs in the vicinity of the tumor as a result.
- **Metastasis:** Tumor cells colonize other tissues far from the original tumor site.

This abnormal tumor cell behavior in tissue aggregates is due to four pathogenetic causes.

1. **Loss of thigmotaxis** (thigmo = greek touch; taxis = movement): Tumor cells navigate using certain proteins of the extracellular matrix (laminin, fibronectin), and propagate along certain tissue structures such as nerve sheaths and collagen fibers.

2. **Loss of contact inhibition:** As soon as normal cells come into contact with each other, they cease to migrate or divide. This is known as contact inhibition. The termination signal initiating this inhibition is received by surface structures such as adhesion molecules (integrins, cadherins). These structures transmit the signal via second messenger substances to the cell nucleus, which controls proliferation. The impaired transmission of this termination signal in malignant tumor cells interrupts intercellular communication, causing tumor cells to continue to proliferate to the extent that they kill each other off.

3. **Loss of intercellular cohesion:** Tumor cells leave their cellular aggregate for two reasons.

- Tumor cells repel each other because of their negative surface charge produced by the carboxyl groups of their membrane-bound sialic acid.
- Loss of adhesion occurs due to the mutation of certain suppressor genes. These genes change the adhesion molecules and result in loss of intercellular cohesion.

4. **Loss of cellular “staying put”:** Tumor cells either secrete proteases, or force the host cells to do so. Involved therein are cysteine, serin-, and metalloproteinases, which dissolve primarily those epithelial and vascular basement membranes containing collagen. These proteases are restrained by tissue inhibitors of metalloproteinases, a factor absent in invasive tumors. In the final stage, the tumor cells up-regulate tumor cell migration factors like HGF, and exit the primary cellular mass, aided by migration furthering extracellular matrix cleavage products.

### **Metastasis**

Metastasis is the movement of tumor cells (the same histologic structure) on the distance from the primary tumor.

**Pathways of metastasis:**

- lymphogenous,
- hematogenous,



- tissue,
- combined.

Stages of metastasis (lymphogenous, hematogenous) include:

**Loss of metastasis-suppressor genes:** Metastasis is prevented by metastasis suppressor genes.

The encoded products of these genes have several functions.

- Cadherins promote intercellular adhesion.
- Tissue inhibitors of metalloproteinase (TIMP) prevent tumor cells from using metalloproteinases to breach the barrier of the vascular basement membrane.
- pNM23 (nonmetastatic gene 23): The product of this gene has to do with nucleoside diphosphate kinase activity. Its role in metastasis is unclear. These genes only cease to function in the latter stages of neoplastic disease.

**Loss of cohesion:** At the beginning of metastasis, the tumor cells lose genes that encode the adhesion molecules (integrins) that cling to proteins of the extracellular matrix (collagen, laminin, and fibronectin) and those that encode the cell's "adhesive" receptors that match the matrix proteins.

**Intravasation**

**Tumor cell embolism**

**Circumvention of immune surveillance:** This is achieved by reduced expression of HLA selfrecognition molecules on the surface of the tumor cell and by the tumor cell acquiring a fibrin coating in the blood vessel (tumor embolus).

**Tumor cell implantation in capillary wall**

**Extravasation**

**Colonization:** Tumor cells colonize certain organs because they detect organ-specific adhesion molecules and because of the presence of a target address on the surface of the tumor cell in the form of lectins.

**Proliferation of metastatic tumor cell.**

**Cachexia** is a condition of abnormally low weight, weakness and general bodily decline associated with chronic disease. It occurs in such conditions as cancer, pulmonary tuberculosis, and malaria.

## **Types of atypism**

### 1. **Morphologic atypism**

**Tissue atypism.** It is a change between parenchyma and stroma. It is predominantly characterized by prevalence of parenchyma. It is characteristic of **benign tumors**.

**Cellular atypism.** It is manifested by cellular and nuclear polymorphism. It is characteristic of **malignant tumors**.

### 2. **Antigenic atypism**

There are five groups of antigens associated with tumor (according to G.I. Abelev)

- Ag of viral tumors
- Ag induced by carcinogens
- Embryonic Ag (oncofetal) → alpha-1,2-fetoprotein
- Iso-Ag of transplantation type
- Heterogenic Ag, organospecific Ag usual in other organs (renal Ag in the tumor of liver)

### 3. **Functional atypism**

It means the loss of functions, an increased or perverted function, functioning inadequacy of tumor tissue to control influences (e.g. synthesis of calcitonin by breast cancer cells, ACTH or ADH synthesis by the lung cancer cells).

### 4. **Metabolic atypism**

It means metabolic changes in tumor tissue. It promotes proliferation and adaptation to oxygen deficiency

- an increase in oncoprotein synthesis — it promotes appearance of specific biologic features; uncontrolled proliferation, loss of the cell clock, immortalization
- synthesis of embryonal proteins and isoenzymes of some enzymes

### 5. **Energy atypism**



Change in the pathway of energy supply activation of anaerobic glycolysis in tumor cells. Pasteur's effect is characteristic.

#### 6. Atypism of proliferation

uncontrolled proliferation

- absence of the contract inhibition of proliferation
- loss of cell clock
- immortalization

#### Differences between benign and malignant tumors

	Benign tumors	Malignant tumors
<b>Growth</b>	Slow with <ul style="list-style-type: none"> <li>• Expansion, displacement</li> <li>• Compression</li> </ul> Compressive atrophy of surrounding tissue	Rapid with <ul style="list-style-type: none"> <li>Destruction</li> <li>Infiltration</li> <li>Thigmotaxis</li> <li>Vascular invasion</li> <li>Metastases</li> </ul>
<b>Size</b>	Increases slowly; tumor may become very large ("knapsack tumor")	Increases rapidly
<b>Capsule</b>	Present; tumor can be surgically "enucleated" from capsule due to compression of local stroma	Partially or entirely absent; tumor frequently recurs after resection
<b>Maneuverability</b>	maneuverable	non-maneuverable
<b>Histologic findings</b>	Usually a perfect image of the histologic mother tissue with a low mitosis count and absence of necrosis	Primitive image of the histologic mother tissue with a high mitosis count and necrosis
<b>Variability of cell size</b>	Cellular and nuclear isomorphism (cells and nuclei of largely the same size)	Cellular and nuclear polymorphism (cells and nuclei of varying size)
<b>DNA content</b>	Nuclear euploidy (uniform coloration of nuclei) with the exception of endocrine tumors, which exhibit nuclear polyploidy	Nuclear aneuploidy, polyploidy, and polychromasia (varying coloration of nuclei)
<b>Ratio of nucleus to cytoplasm</b>	Normal	Nuclei predominate
<b>Nucleoli</b>	Invisible or small and round	Enlarged and irregular
<b>Clinical course</b>	Usually clinically asymptomatic except for compression symptoms; do not recur or metastasize	Produce a wide range of late symptoms; frequently recur and metastasize, cause cachexia

#### Antineoplastic (antiblastomic resistance) mechanisms

##### 1. Anticarcinogenic (neutralization of carcinogens):

- metabolism by cytochrome P-450;
- conjugation with glutathione;
- scavenging of free radicals by antioxidants.

##### 2. Antitransformational (DNA repair):

- activity of mismatch repair genes;
- activity of the nucleotide excision repair system.

##### 3. Anticellular (elimination of the transformed cells):

- cytotoxic T-lymphocytes;
- NK cells, activated macrophages;
- humoral mechanisms (activation of complement; antibodydependent cellular cytotoxicity).

#### Mechanisms by which tumor cells escape or evade the immune system in hosts:

- selective outgrowth of Ag-negative variants;
- loss or reduced expression of hystocompatibility antigens;

- lack of costimulation;
- immunosuppression (secretion of TGFβ);
- apoptosis of cytotoxic T cells (expression of Fas ligand).

#### **Complications of tumors:**

1. **local**
2. **systemic**

#### **Local Complications**

1. **Stenosis:** Tumors can lead to several compression syndromes.
    - Expansion of the tumor compresses the surrounding tissue and causes stenosis in hollow organs. Complications may include difficulties in swallowing, impaired micturition, disruption of intestinal motility, and also increased intracranial pressure.
    - Infiltration of the tumor can cause congestion in a hollow organ. Complications may include prestenotic dilation of the duct, stasis and congestion of secretions or excretions, and bacterial infestation of the congested area.
  2. **Circulatory Disruption:** Tumor growth that compromises or infiltrates vascular structures produces a variety of lesions.
    - Obstruction of venous drainage is common and successively leads to varicose changes in the walls of the veins and thrombosis.
    - Vascular thrombosis may result from vascular stenosis and/or substances produced by the tumor itself that promote coagulation.
    - Bleeding due to erosion of vascular structures may lead to spitting of blood from the lungs or bronchi (hemoptysis), vomiting of blood (hematemesis), passage of bloody stools (melena), blood in the urine (hematuria), acyclic bleeding from the uterus (metrorrhagia), and hemorrhagic effusions.
  3. **Tumor Necrosis:** occurs as a result of the interplay of several factors. These include:
    - Thrombotic arterial obstruction;
    - Vascular compression by the tumor;
    - Twisting of the tumor pedicle;
    - Cytokines (macrophagic TNF-α);
    - Aggressive tumor therapy.
- Complications of tumor necrosis:**
- Ulceration of the inner or outer body surface may occur, primarily in gastrointestinal, skin, and breast cancer.
  - Perforation of the tumor necrosis may occur into hollow organs or through the surface of the skin.
  - Fistulas may form that communicate with adjacent organs.
4. **Disruption of Organ Function:** occurs especially in tumors that not only mechanically alter the organ parenchyma and its supporting tissue but also destroy them. Particularly susceptible tissues include:
    - Neurovascular structures;
    - Urinary tract,
    - Intestinal tract;
    - Skeletal system, where bone tumors can cause pathologic fractures.

#### **Systemic Complications**

1. **Tumor Metastases:** occasionally occur even in the early phases of neoplastic disease.
2. **Cancer Cachexia:** involves weight loss in cancer patients. **Causes include:**
  - **Impaired swallowing** due to the tumor;
  - **Impaired digestion** due to the tumor;
  - **Generation of TNF-α** by macrophages stimulated by tumor-associated antigens.
  - **Generation of leptin** (fat-cell hormone). This results **in loss of appetite (anorexia)**, reduced intake of nutrients, decreased body fat, and increased energy consumption.

3. **Tumor Anemia:** produces the characteristic pale skin of cancer patients. It is due to several factors, including:

- Blood loss due to internal bleeding;
  - Lack of substances that promote maturation of blood cells;
  - Autoreactive antibodies against erythrocytes;
4. Displacement of bone marrow by tumorous infiltrates.

**Paraneoplastic Syndromes** — collective term for a group of generalized pathologic manifestations that are not attributable to the local effects of a tumor but are linked to the existence of a tumor and can regress after the tumor has been removed.

**Pathogenesis:** Often unclear.

- Cell destruction occurs due to formation of autoreactive antibodies against tumor antigens and “self” antigens and as a result of apoptosis caused by certain tumor proteins.
- Dysfunction results from synthesis of peptides with endocrine and enzymatic effects.

#### **Endocrinopathies**

General pathogenesis: Tumors synthesize ectopic hormones of substances similar to hormones. The most important forms are as follows:

- Cushing’s syndrome is caused by formation of ACTH ( in patients with bronchial cancer).
- Flush’s syndrome is caused by formation of serotonin and leads to facial erythema, diarrhea, colic, and bronchospasm (in patients with bronchial or ileal carcinoid).
- Schwartz-Bartter’s syndrome is caused by formation of proteins resembling ADH and leads to hyponatremia (in patients with small cell bronchogenic carcinoma).
- Hypercalcemia syndrome is caused by formation of parathormone-like protein (in patients with squamous cell bronchogenic carcinoma or renal cell carcinomas).

#### **Nerve and Muscle Syndromes**

Pathogenesis: Nerve cells and/or muscle fibers are destroyed by autoimmune processes and by tumor-induced apoptosis. The most important forms are as follows:

- Myasthenia gravis occurs in patients with thymus tumors (thymomas).
- Limbic encephalopathy occurs in patients with small cell bronchogenic carcinoma.
- Degeneration of the cerebellar cortex occurs in patients with small cell bronchogenic carcinoma, breast cancer, or ovarian carcinoma.

#### **Vascular and Hematologic Changes**

- Hemolysis: The tumor synthesizes cytotoxic substances and/or autoreactive antibodies, damaging the bone marrow and leading to hemolytic anemia ( in patients with leukemias or Hodgkin’s disease’s lymphoma).
- Erythrocyte proliferation: The tumor synthesizes substances that stimulate erythropoiesis (erythropoietin), leading to polyglobulism (an overabundance of erythrocytes) (in patients with renal cell carcinoma).
- Leukocyte proliferation: The tumor synthesizes substances that stimulate myelopoiesis, leading to a leukemoid reaction (in patients with stomach cancer or large cell bronchogenic carcinoma).
- Macroscopic coagulopathy: The tumor synthesizes thromboplastic substances that lead to thrombosis (in patients with pancreatic or adenoid carcinomas).
- Disseminated intravascular coagulation: The tumor synthesizes thromboplastic and fibrinolytic substances that consume the clotting factors ( in patients with leukemias).

#### **Dermatologic Disorders**

- Acanthosis nigricans manifests itself as thickening of the skin with clearly discernible papillary lines, hyperpigmentation, and wart-like papillomas (in patients with stomach cancer or squamous cell bronchogenic carcinoma).
- Bazex’s syndrome (paraneoplastic acrokeratosis) manifests itself as reddish purple plaques of calcification on the hands, feet, nose, and ears (in patients with carcinoma of the tongue or tonsils).
- Erythema gyratum repens is a rare skin rash resembling zebra stripes that changes daily (in patients with various carcinomas).
- Hypertrichosis lanuginosa is a rare manifestation involving excessive growth of the head and body hair (in patients with various carcinomas).

**Questions for self-control of knowledge:**

1. What is a cancer?
2. What are signs of morphological atypism tumors?
3. What are signs of metabolic atypism tumors?
4. What are ways of metastasis of tumor cells?
5. Metastasis is an active or passive process?
6. What are mechanisms for development of cachexia in tumors?
7. What are major differences between malignant and benign tumors?
8. What is influence of endocrine and nervous systems in development of tumors process?
9. What is a precancerous?
10. What pathological processes are precancerous state?
11. What is a cancer-causing factors?
12. What is role of viruses in development of tumors?
13. What is mutation theory of carcinogenesis?
14. What are similarities between anti-tumor and transplantation immunity?
15. What is "immune surveillance"?
16. What are possible causes of tumor escape from immune surveillance?
17. What is role of heredity in development of tumors?

**Tasks for self-managed student work:**

1. Role of immunodeficiency states in onset of tumors.
2. Mechanisms of action of oncoproteins.
3. Thermal and mechanical factors in onset of tumors
4. Paraneoplastic syndromes.
5. Principles of pathogenetic therapy of malignant neoplasms.

**Literature****Basis literature:**

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