Paraneoplastic Syndromes — Carcinogenesis

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Paraneoplastic syndromes are rare disorders caused by a change in immune system response to a neoplasm. It is a disorder that produce a nonmetastic impact on systemic organs due to production of substances by the remote tumor cells in the body. Carcinogenesis, also known as tumorigenesis which stands for the process of transforming a normal cell into a cancerous cell. Strictly defined carcinogenesis represents the initiation of a tumor-forming process, while oncogenesis represents maintenance of the tumorous state in cells that have already changed into a cancerous state. The process is largely dependent on the imbalance between proliferation and programmed cell death (apoptosis) in the cell division pattern.

Cellular Pathology of Paraneoplastic Syndromes

Cellular pathology is a branch of pathology that entails the study of cellular injury, cell adaptation, cell aging, and cell death.

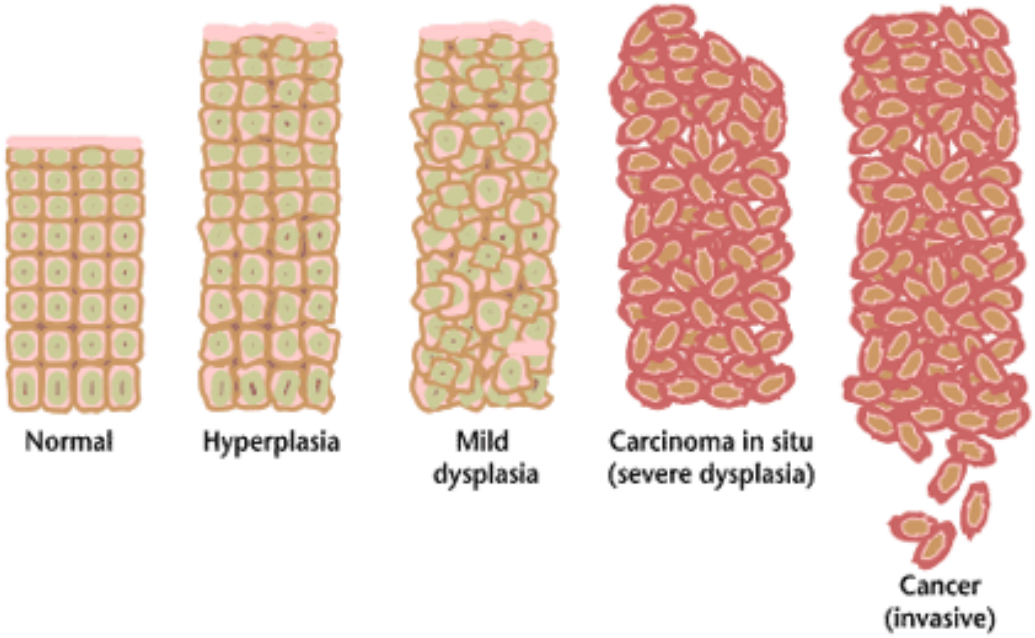
Clinical care

It is also a branch of clinical care that deals with the **examination of tissues and organs from patients for their histological diagnosis**. The tissues are mainly examined for abnormal features that mainly represent carcinogenesis, but additional non-

carcinogenic findings of various cellular characteristics are also documented.

The procedure begins with obtaining the specimen from the patient via a consented procedure such as surgery in an operating theatre, simple procedure in an outpatient clinic and endoscopy samples or tissues. The obtained specimens are then stored in preserving solutions, such as paraffin and formalin, to avoid degeneration, destruction, or loss of specimen quality.

Thin **slices of up to 0.004 mm in thickness are made from the tissues which are later fixed on microscope slides, stained, and observed under a microscope** for features of carcinogenesis. Additional characteristics of stain uptake depending in the present molecular markers are also assessed to characterize the pathology further.



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The common findings of histopathological reports are features that show the inability of the cell to adapt to cellular injury (DNA damage) and other cancer-causing changes. The findings may also represent **various stages of cell adaptation:**

- Hyperplasia
- HypertrophyAtrophy
- Metaplasia

Carcinogenesis

Also known as tumorigenesis which stands for the process of transforming a normal cell into a cancerous cell. Strictly defined carcinogenesis **represents the initiation of a tumor-forming process while oncogenesis represents maintenance of the tumorous state in cells** that have already changed into a cancerous state. The process is largely dependent on the imbalance between proliferation and programmed cell death (apoptosis) in the cell division pattern.

The process is influenced by a variety of risk factors that are considered etiological factors of cancer. They are known as carcinogens and they exert their effects by one of the **two methods**:

1. Epigenetic i.e. they promote uncontrollable growth that leads to cancer.
2. Genotoxic i.e. they induce direct DNA damage and hence genetic mutation that leads to
   tumor formation.

Classification

Primary determining factors that work to initiate DNA mutation/damage that kicks off the tumor-forming process. These are the molecular etiologies of cancer which are radiation, carcinogenic viruses, chemicals such as asbestos and tar, hormonal influence, lifestyle changes such as smoking, alcohol intake and sun exposure, and immunologic factors.

Secondary determining factors which represent genetic transformation that increases the risk of developing cancer. This has been observed in hereditary tumors such as retinoblastoma and nephroblastoma.

Favoring factors which are risk factors that have been associated with increased incidence of malignant tumors such as geographical distribution, nutrition, age, and sex. These factors affect the function of various genes and lead to the formation of abnormal genes that are central to the formation of a tumor.

Important types

Proto-oncogenes

Proto-oncogenes are genes that **control the normal cell division**. They are targeted by carcinogenic toxins for induction of mutations that may arise from viruses, chemicals, and spontaneous mutations.

Oncogenes

Upon sustaining various mutations, proto-oncogenes become oncogenes which are the tumor causing genes due to their uncontrollable cell division properties. Examples of oncogenes **include the K-ras gene found in colon cancer**.

Tumor suppressor genes

Tumor suppressor genes are genes that **control the rate of cell division and protein synthesis**. In simple terms, they put the oncogenes in check. In carcinogenesis, there is increased expression of carcinogens and reduced tumor suppressor genes expression. Examples of tumor suppressor genes include the p53 gene found in cancer of the breast colon and stomach.

DNA mismatch repair genes

DNA mismatch repair genes are thought to be found in tumor cells thus giving them some level of risk to spontaneous mutations. They are **easily triggered by mutation by carcinogenic materials.**

Multistage carcinogenesis theory

It puts forward that **carcinogenesis is a protracted process involving various stages that begin with damage to cellular DNA** and comptonization of the cells ability to repair this damage. These interventions require a lot of time to take effect and hence the long latency period for cancer formation before the tumor is clinically evident.

Initiation

This is the stage where there is the interaction of a normal cell with a carcinogen to induce genetic mutation/DNA damage. This damage can be repaired or reproduced by the cell division mechanisms. The **most common outcome at this stage is repaired by the body and thus this step rarely leads to malignancy** more so if the injury is the first attempt. However, if the body fails to repair the damage, the body continues reproducing the error/damage and this leads to more errors/damage and eventually cancerous states. Genotoxic factors such as viruses, radiation, and chemicals (asbestos) initiate this process.

Promotion

Here, the cells with chronic genetic mutations lead to the autonomic production of the cells leading to a faster division of already mutated cells. This leads to further spread of the already damaged DNA. The substances that accelerate this process are known as promoters. They may be non-carcinogenic or weakly carcinogenic, but rely on the damage caused by initiating carcinogens. Unlike initiating carcinogens that work by binding to DNA, promoters work by binding to cell membranes. **Examples of promoters include tar in cigarette smoke, alcohol, and carcinogenic hormones**. The rapid division of the affected cells leads to accumulation and formation of a benign mass. The process is still reversible by removal of the carcinogenic triggers and removal of the tumorous cells.

Progression

This refers to a stage **where the abnormal cells exceed the normal cells in the pathogenic region**. The cells are prone to more damage that increases the damage and rate of cell division paving a way to the next stage of carcinogenesis.

Malignant conversion

The **last stage where the tumor acquires invasive and metastatic properties** causing damage and symptoms consistent with cancer.

The genetic mutation theory

It holds that mutations arise from structural abnormalities of genes regulating cell division. The **mutations are then carried down to daughter cells leading to initiation of the cancer formation process**. The theory is supported by the fact that most genetic diseases pose an increased risk of developing cancer. For example, patients with Down’s syndrome and Klinefelter’s syndrome have an increased risk of developing leukemia. Moreover, most tumors have an incriminated genetic mutation that is pathognomonic of the disease such as retinoblastoma and nephroblastoma.

The aberrant differentiation theory

It puts forward that **cancer emanates from functional disorders of genetic mutation with no structural changes seen**. This theory is supported by laboratory demonstration that incubation of cancer cells in an environment with cells free of cancer leads to reversal of the tumorigenesis; thus, this theory views cancer as an epigenetic and reversible process influenced by nearby situations.

Viral theory

Viral oncogenes are thought to be solely responsible for triggering the oncogenesis. They induce carcinogenesis by interaction and damage of the cellular DNA.

Cell selection theory

It views carcinogenesis as a mere increase in the rate of cell division and downplays the presence or the impact of genetic mutations in oncogenesis.

Paraneoplastic Syndromes

These are disorders that **occur because of an immunologic response to the presence of a neoplasm in the body**. They are also described as clinical syndromes that arise from substances produced by the tumor and not by a direct effect of the tumor such as metastasis, mass effects or invasiveness of the tumor.

Etiology

In most situations, the link between the tumor and the paraneoplastic syndrome is not well understood, but it is thought to **arise from hormones, peptides or cytokines produced by the tumor such as ACTH and ADH.**

Epidemiology

Paraneoplastic syndromes are seen in all patients with tumors, but they are more common in the middle-aged patients. They have no racial or sexual predisposition. The common cancers that present with paraneoplastic syndromes include cancer of the lung breast, ovaries, kidney, liver, stomach, and lymphomas.

The neoplastic syndromes are found in 10-15% in all malignancies. Neurological paraneoplastic syndromes are seen in 1% of cancer patients.

Note: Up to 20% of cancer patients experience paraneoplastic syndrome, but only a few are detected. Most of the paraneoplastic syndromes are noted after diagnosis of the tumor, but few of them preceded the diagnosis of cancer. Neurologic paraneoplastic syndromes are thought to be present in 1% of the general population.

Pathophysiology

With the occurrence of tumor cells, body tries to fight against it to destroy it by production of antibodies as an immune response. These **antibodies cross-react with normal body tissues that possess similar proteins as the tumor cells leading to the development of a paraneoplastic syndrome**. Another theory for the pathogenesis of the syndromes is from the hormones produced by the tumor, such as a posterior pituitary tumor secreting antidiuretic hormone that is meant to produce interference with the normal body mechanisms. These hormones are known as tumor markers that are diagnostic of the disease.

Presentation and classification

Paraneoplastic syndromes are classified into various systemic syndromes that have varying symptoms as follows:

Endocrine paraneoplastic syndromes

They include syndrome of inappropriate ADH secretion that is evident in small cell lung cancer and central nervous system malignancies. Their symptoms are hyponatremia, hypokalemia, headaches, weakness and altered mental status.

Cushing syndrome is seen in pancreatic carcinoma and thymoma. It may be present with hypokalemia. Its symptoms are moon facies, truncal obesity, and gynecomastia. Hypercalcemia is seen in lung, breast, and renal carcinoma.

Carcinoid syndrome is evident with a secretion of serotonin and bradykinin in cancer of the bronchus.

Hematological paraneoplastic syndromes

- Anemia.
- Granulocytosis that may lead to itching.
- Trousseau sign is seen in pancreatic carcinoma and bronchial carcinoma.
- Thromobocytosis
- Disseminated intravascular coagulation
- Cryoglobulinemia in lung cancer

Neurological paraneoplastic syndromes

Lambert Eaton myasthenic syndrome manifests xerostomia, sexual impotence, myopathy, and peripheral neuropathy. Paraneoplastic cerebellar degeneration was seen in lung cancer, ovarian cancer, and breast cancer that presents with features of depression, seizures, and memory loss.

Other syndromes are:

- Polymyositis and limbic myelitis
- Paraneoplastic limbic encephalitis characterized by depression, seizures, irritability and memory loss.
- Neuroblastoma
- Myasthenia gravis

Mucocutaneous paraneoplastic syndromes

- Acanthosis nigricans and a sweet syndrome that leads to the development of flushes, alopecia, and migratory thrombophlebitis.
- Herpes zoster
- Ichthyosis
- Blackish pigmentation of skin known as dermic melanosis

Rheumatological paraneoplastic syndromes

- Rheumatoid polyarthritis
- Polymyositis and dermatomyositis that presents with muscle enlargement and weakness,
- Osteoarthropathy that presents with painful joints, effusions, and swollen joints are forms of rheumatological paraneoplastic syndromes.
- Scleroderma
- Systemic lupus erythematosus
- Secondary amyloidosis

Renal Syndromes

- Nephrotic syndrome
- Hypokalemia
- Hyponatremia
- Hyperphosphatemia

Overview of paraneoplastic syndromes

Syndrome	Associated Cancer
Acanthosis nigricans	Stomach carcinoma
Eaton-Lambert syndrome (Antibody against calcium channel)	Small cell carcinoma of lung
Hypertrophic osteoarthropathy	Bronchogenic carcinoma
NBTE	Mucus-secreting pancreatic/colorectal carcinoma
Seborrheic keratosis (Leser-Trelat)	Stomach carcinoma
Superficial migratory thrombophlebitis	Pancreatic carcinoma

Investigations

Laboratory work-ups is preferred to determine the functionality of the paraneoplastic syndrome and the best way for management. Paraneoplastic syndrome can be evaluated by following tests :

- A CT scan has opted for the diagnosis and staging of tumors.
- A **MRI offers a better screening of soft tissue and anatomical assessment compared to CT scans.**
- A PET scan is preferred for the evaluation of micrometastasis and response to treatment.
- ESR, Complete blood count, CEA, AFP and other hormones and tumor markers is done to identify antibodies, hormones, infection and possible nutrient disorder in the blood. It is advocated to detect the possible etiology and progress of the disease
- Lumber puncture to obtain a sample of CSF to detect the possible presence of antibodies.

Treatment

Treatment of the tumor causing the paraneoplastic syndrome

- Surgery for excision of the tumor, such as adrenalectomy, is an ACTH producing adrenal mass and thyroidectomy for a functional thyroid tumor.
- Chemotherapy.
- Radiotherapy.
- Combination therapy with any two/three of the above treatment modalities.

Treatment of the paraneoplastic syndrome

Immunosuppression with corticosteroids, such as prednisone, inhibit inflammation. Corticosteroids, such as prednisone, inhibit inflammation. Immunosuppressants slow the production of disease-fighting white blood cells. They include azathioprine and cyclophosphamide.

Plasma exchange to separate blood cells from the fluid part of blood and reduce the immune components. Intravenous immunoglobulin (IVIg). Immunoglobulin contains

healthy antibodies from blood donors. High doses of immunoglobulin speed up the destruction of the damaging antibodies in your blood.

Supportive treatment of other complications or slowing the progress of the paraneoplastic syndrome:

- Anti-seizure medications, which may help control seizures associated with syndromes that cause electrical instability in the brain.
- Fluids.
- Physical therapy. Exercises help in the quick recovery and setting in of complications associated with immobility.
- Speech therapy. It helps in gaining the necessary muscle control in patients with trouble speaking or swallowing.

Course and prognosis

As every individual exhibit different paraneoplastic syndromes from others, so prognosis also vary in great extent. Course and prognosis also **vary with each paraneoplastic syndrome;** disseminated intravascular coagulation do not resolve easily whereas hypertrophic osteoarthropathy show good results with medications. Some of the paraneoplastic disorders may get settled spontaneously. Mortality is mainly marked due to comorbidities such as chronic heart failure and tumor burden itself or kidney failure.

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Notes