



A Cancer Journal for Clinicians

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CA Cancer J Clin 1970;20;35-43

DOI: 10.3322/canjclin.20.1.35

This information is current as of October 18, 2010

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Medical Syndromes Associated With Malignant Tumors

David Schottenfeld, M.D.

Careful and persistent study is needed to distinguish the clinical and biochemical features of malignant tumors that do not arise from the mechanical effects of metastatic or locally invasive disease, nor from the iatrogenic effects of therapeutic manipulation. In some instances, these multisystemic manifestations dominate the clinical presentation of the cancer so that awareness and recognition of their significance and degree of specificity will facilitate earlier diagnosis and proper treatment. These symptom complexes and metabolic aberrations do not necessarily signify dissemination or inoperability, except for those syndromes which are usually associated with a predominately undifferentiated and rapidly proliferating tumor.

Apart from their clinical significance, these syndromes have profound biologic implications. In regard to the endocrine syndromes, there is presumptive evidence that a tumor arising from nonendocrine tissue synthesizes peptides and proteins with hormonal activity. These paradoxical hormonal effects are believed to arise from the derepression or activation of latent coding functions in the DNA of tumor

cells. In regard to the association with diseases of connective tissue, neuromyopathies, and multifocal leukoencephalopathy, it has been suggested that these conditions develop from auto-immune or altered immune responses to organ-specific antigens which are elaborated by the malignant tumor. The association of auto-immune diseases and congenital immunologic deficiency syndromes* with lymphoreticular malignancy emphasizes the *pathogenic* significance of immunologic dysfunction in lymphoma patients. The following tables list some of the multisystemic abnormalities associated with cancer.

* *Examples of inherited diseases which are characterized by immunologic deficiency and the predisposition for malignancies of the reticuloendothelial system include:*

1. *Wiskott-Aldrich syndrome characterized by sex-linked recessive inheritance, recurrent infections, chronic eczema and thrombocytopenia;*
2. *Congenital sex-linked agammaglobulinemia of Bruton; and*
3. *Ataxia telangiectasia of Louis-Bar, which is a chronic and progressive multi-system disease with autosomal recessive inheritance, recurrent infections, oculocutaneous telangiectasia, mental retardation, progressive ataxia, choreo-athetosis and nystagmus.*

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EXAMPLES OF MEDICAL SYNDROMES AND DISORDERS ASSOCIATED WITH MALIGNANT TUMOR

Associated Diseases	Tumor Sites
A. <u>Cutaneous, Connective Tissue and Osseous Diseases</u>	
1. Dermatomyositis	Lung, Breast, Stomach, Ovary, Colon and Rectum, and Lymphoma
2. Scleroderma (Systemic Sclerosis)	Alveolar Cell (Terminal Bronchiolar)
3. Disseminated Lupus Erythematosus	Hodgkin's Disease, Lymphosarcoma, Chronic Lymphocytic Leukemia
4. Hypertrophic Pulmonary Osteoarthropathy with or without Synovitis	Bronchus, Pleura (Mesothelioma), Metastatic Intrathoracic Tumors
5. Acute Arthritic Symptoms	Prostate
	Acute Lymphatic Leukemia
	Multiple Myeloma
	Acinar Cell of Pancreas
6. Malignant Acanthosis Nigricans	Intraabdominal Adenocarcinomas (i.e., Stomach), Carcinoma of Lung and Thyroid, Lymphosarcoma

Comments

Approximately 50 percent of patients over age 40 presenting with this disease will have an associated malignancy.

Pulmonary fibrosis and reactive proliferation of terminal bronchiolar and alveolar epithelium were prominent.

Prompt relief of symptoms after resection of tumor, denervation of lung root or sectioning of vagus nerves. Clubbing may be present without osteoarthropathy, but periostitis without clubbing would be most unusual.

Articular signs include erythema, swelling, tenderness of the metacarpophalangeal and/or interphalangeal joints that respond to therapy with estrogens.

(In Children)

May be accompanied by amyloid deposition in synovial tissue. Presentation with "carpal tunnel syndrome." Consider also secondary gouty arthritis.

With subcutaneous fat necrosis.

Characterized by hyperpigmentation, papillomatosis and hyperkeratosis of the axillae, groins, anogenital area, lateral and posterior aspects of the neck. Less frequently, palms, soles, antecubital and popliteal spaces and mucous membranes are involved.

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Associated Diseases	Tumor Sites
B. Neuromuscular Disorders (Not due to metastatic disease)	
1. Parenchymatous Cerebellar Degeneration	Lung, Ovary, Breast and Uterus predominating
2. Encephalomyelopathy	Lung, Hodgkin's Disease, Kidney, Breast and Pancreas predominating
3. Multifocal Leukoencephalopathy	Leukemia, Hodgkin's Disease, Lymphosarcoma
4. Polyneuropathy, Motor, Sensory or Mixed	Lung, Multiple Myeloma, Hodgkin's Disease, Leukemia, Pancreas, Stomach, Colon and Rectum, Breast and Ovary
5. Carcinomatous Myopathy	Lung (usually oat cell or small cell carcinoma), Prostate, Breast, Rectum and Ovary predominating
6. Myasthenia Gravis	Thymoma

Comments

Loss of Purkinje cells throughout cerebellar cortex.
Degeneration of dorsal spinocerebellar tracts,
superior cerebellar peduncles, posterior columns
and corticospinal tracts as well.

Ophthalmoplegia, bulbar palsy, pyramidal tract
signs, anterior horn cell disease and organic mental
syndrome

Demyelinating lesions of the cerebral hemispheres,
brain stem, cerebellum.

Idiopathic degeneration of meninges, nerve roots,
dorsal root ganglion cells and peripheral nerves.
The Lymphomas and Leukemias may be
associated with a multifocal leukoencephalopathy
characterized by progressive demyelinating lesions.
There may be a Landry-Guillian-Barre ascending
paralytic polyradiculoneuropathy.

15-30 percent coexistence of thymoma. Aregener-
ative anemia, acquired hypogammaglobulinemia
and Cushing's syndrome also noted in association
with thymic tumors.

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Associated Diseases

Tumor Sites

C. Endocrine Effects and Associated Metabolic Disorders

- | | |
|--|---|
| 1. Hyperadrenocorticism With Or Without The Classic Features Of Cushing's Syndrome | Bronchus (Oat Cell), Thymus (Epithelial Type), Bronchial (Carcinoid), Thyroid (Medullary), Pancreas (Acinar and Islet Cell; may be associated with the Zollinger-Ellison syndrome and hypoglycemia) |
| 2. Inappropriate Secretion Of Antidiuretic Hormone | Bronchus (Oat Cell) predominating |
| 3. Hypoglycemia And Extra-pancreatic Tumors | Fibrosarcoma, either intrathoracic or retroperitoneal, Mesothelioma, Other mesoderm tumors of large size, Primary hepatoma, Other epithelial tumors of large size. |
| 4. Hypercalcemia And Hypercalciuria Not Due Solely To Osseous Metastases. | Lung, Breast, Kidney, Ovary, Pancreas, Colon. |
| 5. A. Carcinoid Syndrome (Argentaffin and Non-Argentaffin Tumors) | A. Small Intestine, Bronchus (Adenoma), Appendix, Colon and Rectum, Duodenum, Ovary, Gall Bladder, Pancreas (Acinar and Islet Cell), Thyroid, and Bronchus (Oat Cell) |
| B. Atypical Carcinoid Syndrome With Increased Secretion Of 5-Hydroxytryptophan And Histamine | B. Stomach, Pancreas, Bronchus (Oat Cell). |
| 6. Thyroid Dysfunction | Hydatidiform Mole and Choriocarcinoma |

Comments

The plasma or tumor of a number of these patients contains an increased amount of an ACTH-like substance and frequently melanocyte-stimulating hormone. A significant number of patients demonstrated bilateral adrenocortical hyperplasia, severe hypokalemic alkalosis, skin pigmentation, edema and diabetes mellitus.

A syndrome characterized by hyponatremia and failure of sodium conservation by the kidneys. Markedly decreased serum osmolality and a persistently hypertonic urine. In the absence of appropriate water restriction the positive water balance may eventually lead to water intoxication: lethargy, confusion, seizures and coma. Isolation of antidiuretic activity from the tumor has suggested intrinsic synthesis.

Important mechanisms responsible for hypoglycemia would include:

- (1) the large size of the tumor with increased utilization of glucose
- (2) secretion of an insulin-like substance and (3) deficient glucogenesis

Only presumptive evidence that the tumor is elaborating a hypercalcemic agent or parathyroid hormone-like substance. Clarification awaits a sensitive and specific assay for parathyroid hormone.

Pathophysiologic effects attributed to excess elaboration of serotonin and/or kinin peptides potentiated by hepatic metastases. Carcinoid syndrome is characterized by cutaneous flushing, tachycardia, chest, abdominal or leg pain, hyperperistalsis, broncho-constriction, valvular heart lesions (endocardial fibrosis and plaque formation) resulting in pulmonary stenosis, tricuspid insufficiency or left-sided cardiac involvement, and pellagroid skin lesions with intestinal malabsorption.

Associated with increased plasma concentration of thyroid stimulating hormone and not simply increased protein-binding of thyroid hormone. In several instances extracts of tumor tissue contained thyrotrophin activity. Most patients do not manifest hyperthyroidism.

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Associated Diseases	Tumor Sites
7. Gynecomastia	Associated Cancers: Lung, Kidney, Stomach.
<u>Vascular and Hematologic Manifestations</u>	Cerebellar hemangioblastoma*, Hypernephroma*, Hepatoma, Pheochromocytoma*, Uterine fibroma. Benign renal lesions: cyst, adenoma. Virilizing Ovarian Tumors
1. Polycythemia	*May occur in the same patient with <u>angiomas of the retina</u> of the von <u>Hippel-Lindau syndrome</u> .
2. Migratory Thrombophlebitis	Associated cancers: Lung, Pancreas, Prostate, Ovary, Stomach, Colon and Rectum predominate

Comments

Concomitantly, in lung cancer, most of the patients have hypertrophic osteoarthropathy. In some instances gonadotrophic activity has been demonstrated in the tumor tissue accompanied by high levels in the plasma and urine and increased excretion of urinary estrogens. As with clubbing, however, gynecomastia may be a concomitant manifestation of non-neoplastic pulmonary diseases.

Elaboration of erythropoietin-like material by the tumor tissue with stimulated erythropoiesis. Whereas patients with polycythemia vera usually have thrombocytosis, leukocytosis and splenomegaly, in addition to the increase in the total volume of circulating red cells, the tumor-associated erythrocytosis group usually do not.

Cancer cells have not been found in the veins at the site of the thrombotic lesions. Nonbacterial thrombotic (marantic) endocarditis with arterial embolization, fibrinolytic purpura, consumption coagulopathy and cryofibrinogenemia are infrequently of assistance in early diagnosis.

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