Paraneoplastic Syndromes

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Abstract :

Introduction : Paraneoplastic syndromes are caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy or side effects of cancer treatment. **Pathogenesis :** These syndromes may be due to tumor secreting substances, depletion of normal substances or host response to the tumor. **Classification :** These syndromes are empirically divided into endocrine, hematologic and nervous system. **Diagnosis & Treatment :** Comprehensive history, physical examination and antibody testing are useful for diagnosis. Treatment is directed towards primary etiology with or without immunosuppression. Some syndromes are irreversible.

Key Words: Paraneoplastic syndromes, cancer

Introduction :

Paraneoplastic syndromes are a group of clinical disorders caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy or side effects of cancer treatment. Symptoms and signs of paraneoplastic syndromes are not attributable to direct effect of cancer. These syndromes may be the first symptom of underlying malignancy and may or may not recover with the treatment of the underlying etiological diagnosis.

Pathogenesis :

Before establishing the diagnosis of paraneoplastic syndrome, it is a rule to disprove that the symptoms or signs are related to the direct effect of the neoplastic mass. These syndromes may be due to tumor secreting substances, depletion of normal substances or host response to the tumor.

Classification :

These syndromes are empirically divided into those of endocrine, hematologic and nervous system.

I. Endocrine system

Either endocrine failure or excess production of hormones secreted by cancers can produce endocrine syndromes or ectopic hormone syndromes. Few well established syndromes that commonly seen are,

1. Ectopic ACTH Syndrome

Tumors produce ACTH or an ACTH-like substance that leads to adrenal hyperplasia and hypercortisolism. The gene involved is the proopiomelanocortin gene that produces ACTH and other related substances.[1] Ectopic ACTH production is commonly associated with small-cell lung cancer (SCLC) and also in a variety of neoplasms.[2] Differential diagnosis include Cushing's disease, adrenal dysfunction, ectopic ACTH production, and corticotropin-releasing hormone (CRH) overproduction; further differentiation should be considered with 24-hour urinary cortisol, low dose or high dose dexamethasone suppression test.

Surgery (bilateral adrenalectony) is effective in treating early stage Cushing's syndrome. Lifelong glucocorticoid and mineralocorticoid replacement is required. Mitotane, aminoglutethimide, metyrapone, or ketoconazole might be useful in ACTH suppression as might be octreotide.[3]

2. Syndrome of Inappropriate Antidiuretic Hormone Production (SIADH)

The principal malignancy associated with SIADH is SCLC in 75% of cases; others include non small-cell lung cancer & head and neck cancers. Patients with SIADH have normal volume status, hyponatremia with hypoosmolality, elevated renal sodium excretion with urine osmolality more than plasma osmolality. Differentials include central nervous system diseases (stroke, acute psychosis, inflammatory and demyelinating disorders, seizures, infections, and hemorrhage), lung diseases (pneumonia, tuberculosis, acute respiratory failure), and drug effects.[4] Treatment includes water restriction, hypertonic saline or demeclocycline depending on severity of symptoms.

3. Hypocalcemia

Tumors with bone metastases such as breast, prostate, and lung cancers can lead to hypocalcemia. Calcitonin secreting cancers (i.e., medullary carcinoma of the thyroid

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and rarely breast cancer, colorectal cancer, SCLC, and carcinoid) also cause hypocalcemia. [5] Rapid correction of serum calcium depending upon symptoms, repletion of serum magnesium, and treating vitamin D deficiency also warranted.

4. Hypoglycemia

Common causes are mesenchymal tumors, hepatic carcinomas and insulinomas. Production of insulin-like growth factors 1 and 2 and ectopic insulin release are the main underlying mechanisms. Treating underlying disease or use of glucagons, high-dose corticosteroids, or somatostatin analogues might be useful. [6]

II. Hematological syndromes

Usually seen are normocytic normochromic or hypochronic anemia of chronic disease; anemia secondary to marrow invasion, chemotherapy and radiation treatment. *Normocytic normochromic is a common paraneoplastic syndrome. Pure red cell aplasia* can occur in thymoma and large granular lymphocytic lymphoma. Immune hemolytic anemias can occur in chronic lymphocytic leukaemia. Others include *erythrocytosis* in renal cell carcinoma, wilm's tumour, adreno-corticol tumour and virlising tumours. Granulocytosis or granulocytopenia, eosinophilia and basophilia, platelet disorders and coagulopathies including acquired von Willebrand disease or disseminated intravascular coagulation (DIC) are usually diagnosed with lymphomas and myeloprolifertive disorders or sometimes with solid tumours like breast, gastrointestinal and lung cancers. Treatment of the underlying disease and supportive care is essential.

III. Nervous system

Onset is usually acute or sub acute which is followed by stabilization within a few weeks. Any part of nervous system may be affected. These syndromes may occur before the presence of systemic cancer is known. Diagnosis is supported by frequent detection of antibodies in serum and CSF (cerebrospinal fluid) reacting with antigens expressed by tumor & nervous system (onconeuronal antigens). Most antibodies associated syndromes affecting CNS are highly specific for presence of cancer. Cytotoxic T-cell responses have been important in pathogenesis of PNS. Presence of prominent infiltrates of CD8+ and CD4+T cells in nervous tissues had been demonstrated.

Autoantibodies and evidence for cell mediated immunity against neuronal, glial, or muscle cell antigens have been identified in a number of paraneoplastic neurologic disorders. [7] The presenting symptoms and/or signs may suggest the part of the nervous system that is affected. In accordance to the involved region antibody testing may be carried out to establish the diagnosis of specific paraneoplastic syndrome. Under are some of the well recognized syndromes.

1. Subacute Sensory Neuronopathy and Encephalomyeloneuritis: Pure sensory neuronopathy with anti-Hu antibodies seen in SCLC. [8]
2. Limbic encephalitis: It's also related with SCLC, and anti-Hu antibodies in majority of patients. Immunosuppression and treating disease is useful.
3. Progressive Cerebellar Degeneration: It is seen in SCLC and patients treated for Hodgkin's lymphoma. Treating underlying cancer might reverse symptoms to little extent.
4. Opthalmologic disease: Vision loss commonly due to photoreceptor degeneration or optic neuropathies. Opsoclonus-myoclonus (OM) is seen in children with neuroblastoma and hodgkin's lymphoma. [9]
5. Neuromuscular Junction Disorders: Myasthenia gravis is associated with thymoma in approximately 15% of cases. [10] Sixty percent of patients with Lambert-Eaton myasthenic syndrome have underlying SCLC. [11]

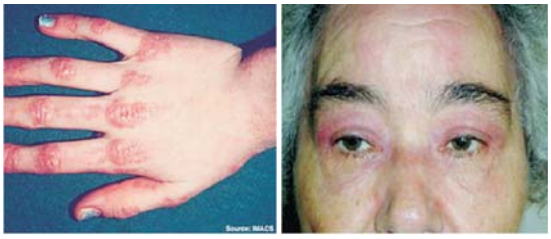
Other neurologic syndromes include peripheral and autonomic neuropathies, movement disorders and stiff syndrome. Various autoantibodies are implicated. Antineoplastic treatment is useful.

IV. Skin and integumentary system.

Acanthosis nigricans is characterized by gray-brown velvety plaques affecting the neck, flexor areas and anogenital region. It is associated with adenocarcinomas of the GI tract, lung, breast, ovarian cancers and hematologic malignancies. *Ichthyosis* is most commonly associated with Hodgkin's lymphoma, multiple myeloma, and Kaposi's sarcoma. *Acrokeratosis paraneoplastica (Bazex's syndrome)* is associated with male gender and squamous cell carcinoma of the esophagus, head and neck, or lungs. Neutrophilic dermatosis (Sweet's syndrome) has an association with malignancy in 20% of cases mostly with acute myeloid leukemia. [12] *Vasculitis* is observed in 4.5% to 8% of malignancies, in solid tumors (most commonly lung non small-cell), small cell carcinoma of the esophagus and prostate, as well as in hematological malignancies. [13] *Migratory thrombophlebitis* has been associated with cancer of GI tract, lung, prostate, ovary, as well as

leukemias and lymphomas. *Paraneoplastic pemphigus* is most frequently seen in B-cell lymphoproliferative disorders, including lymphomas and CLL as well as Castleman's disease, thymoma, Waldenstrom's macroglobulinemia, and spindle cell neoplasms. *Dermatomyositis* has been linked to malignancy in over 25% of cases [14] (Fig.1). *Cowden's disease* is an autosomal-dominant syndrome with very high risk of breast and thyroid carcinomas whereas Gardner's syndrome is characterized by hundreds of adenomatous colorectal polyps, with an inevitable progression to colorectal cancer by age 40. *Necrolytic migratory erythema* is associated with glucagonoma and characterized by epidermal necrosis on the central face, lower abdomen, perineum, and buttocks.

Fig.1 : Dermatomyositis



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V. Other systems that are affected include the kidney and osteochondral disorders in the form of *nephrotic* and *hypertrophic osteoarthropathy* respectively.

Diagnostic and treatment approach

A comprehensive history and physical examination remains the mainstay of diagnosis and characterization of paraneoplastic disorders. MRI and FDG-PET scan imaging serves to identify primary or metastatic disease and monitor response to therapy. CSF analysis is required for neurologic disease. Antibody testing in accordance to the established syndromes should be strongly considered. Treatment approaches concentrate on tumor ablation, either with surgery, radiotherapy or systemic therapies which is more effective than immunosuppression for clinical improvement. Recovery after effective tumor therapy is variable and frequently incomplete.

Conclusion

It is important to timely diagnose paraneoplastic syndrome as it may be the first sign of malignancy, successful treatment may lead to disappearance of symptoms and signs; proteins secreted may be used as tumor markers for follow-up evaluation and, most importantly for the palliation of symptoms.

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