Paraneoplastic Syndrome

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Overview:

- **Definition:**

A paraneoplastic syndrome is a disease or symptom that is the consequence of the presence of cancer in the body, but is not due to the local presence of cancer cells. These phenomena are mediated by humoral factors (by hormones or cytokines) excreted by tumor cells or by an immune response against the tumor. Paraneoplastic syndromes are typical among middle aged to older patients, and they most commonly present with cancers of the lung, breast, ovaries or lymphatic system (a lymphoma). Sometimes the symptoms of paraneoplastic syndromes show before the diagnosis of a malignancy, which has been hypothesized to relate to the disease pathogenesis. In this paradigm, tumor cells express tissue-restricted antigens (such as neuronal proteins), triggering an anti-tumor immune response which may be partially or, rarely, completely effective in suppressing tumor growth and symptoms. Patients then come to clinical attention when this tumor immune response breaks immune tolerance and begins to attack the normal tissue expressing that (e.g. neuronal) protein.

- **Background**

The first report of a paraneoplastic syndrome dates back to the 19th century. The description of the relationship between neurological disorders and systemic tumors has been attributed to a French physician, M. Auchè, who described peripheral nervous system involvement in cancer patients in 1890.

Paraneoplastic syndromes are rare disorders that are triggered by an altered immune system response to a neoplasm. They are defined as clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease.

In a broad sense, these syndromes are collections of symptoms that result from substances produced by the tumor, and they occur remotely from the tumor itself. The symptoms may be endocrine, neuromuscular or musculoskeletal, cardiovascular, cutaneous, hematologic, gastrointestinal, renal, or miscellaneous in nature.

Although fever is the most common presentation, several clinical pictures may be observed, each of which specifically simulates more common benign conditions. These syndromes vary from dermatomyositis-polymyositis to Cushing syndrome to the malignant carcinoid syndrome. A large number of cancer patients show CNS involvement.

Paraneoplastic syndromes may be the first or most prominent manifestation. When a patient without a known cancer presents with one of the "typical" paraneoplastic syndromes, a diagnosis of cancer should be considered and investigated.

- **Importance:**

Paraneoplastic syndromes occur in about 10% - 15% of patients with a malignant disease. Despite their relative infrequency, paraneoplastic syndromes are important to recognize, for several reasons:

1) They may represent the earliest manifestation of an occult neoplasm.
2) In affected patients, they may represent significant clinical problems and may even be lethal.
3) They may mimic metastatic disease and therefore confound treatment.
4) They may serve as a TUMOR MARKER in previously treated patients to detect recurrence, or in patients undergoing ADJUVANT THERAPY to guide further treatment

- **Pathophysiology:**

The pathophysiology of paraneoplastic syndromes is complex and intriguing. When a tumor arises, the body may produce antibodies to fight it by binding to and destroying tumor cells. Unfortunately, in some cases, these antibodies cross-react with normal tissues and destroy them, which may result in a paraneoplastic disorder. For example, antibodies or T cells directed against the tumor may mistakenly attack normal nerve cells. The detection of paraneoplastic anti-neural antibody was first reported in 1965.

In other cases, paraneoplastic syndromes result from the production and release of physiologically active substances by the tumor. Tumors may produce hormones, hormone precursors, a variety of enzymes, or cytokines. Several cancers produce

proteins that are physiologically expressed in utero by embryonic and fetal cells but not expressed by normal adult cells. These substances may serve as tumor markers (eg, carcinoembryonic antigen [CEA], alpha-fetoprotein [AFP], carbohydrate antigen 19-9 [CA 19-9]). More rarely, the tumor may interfere with normal metabolic pathways or steroid metabolism. Finally, some paraneoplastic syndromes are idiopathic.

Classification:

Paraneoplastic syndromes can be generally classified into **neurological** and **non-neurological**, and the *non-neurological* can be further subdivided into several subtypes [*see Table 1*].

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Table 1- Classification of Paraneoplastic Syndromes

Neurological Paraneoplastic Syndromes:

Lambert-Eaton myasthenic syndrome (LEMS):

- **Main causal cancer:** Small-cell lung cancer
- **Causal mechanism:** Immunologic

It is a rare autoimmune disorder that is characterised by muscle weakness of the limbs, hyporeflexia, and dysautonomia. It is the result of an autoimmune reaction, where antibodies are formed against voltage-gated calcium channels in the neuromuscular junction. Around 60% of those with LEMS have an underlying malignancy, most commonly small cell lung cancer; it is therefore regarded as a paraneoplastic syndrome. People who develop LEMS are usually over 40, although it may occur at any age. The diagnosis is usually confirmed with electromyography and blood tests; these also distinguish it from myasthenia gravis, a related autoimmune neuromuscular disease. If the disease is associated with cancer, direct treatment of the cancer often relieves the symptoms of LEMS. Other treatments often used are steroids, azathioprine and intravenous immunoglobulin, which suppress the immune system, and pyridostigmine and 3,4-diaminopyridine, which enhance the neuromuscular transmission. Occasionally, plasma exchange is required to remove the antibodies.

Paraneoplastic cerebellar degeneration:

- **Main causal cancers:** lung, ovarian cancer, breast carcinoma
- **Causal mechanism**: ---

PCD is believed to be due to an autoimmune reaction targeted against components of the central nervous system (specifically Purkinje cells). It is thought to be triggered when tumor cells (most commonly ovarian or breast cancer) express a protein normally expressed in the brain (this is the Purkinje neuronal protein termed cdr2). This is believed to trigger an anti-tumor immune response that may be clinically significant, but also an anti-neuronal immune response. Patients usually complain first of difficulty with walking, which progresses over weeks to months. Diplopia and vertigo may be early symptoms. Loss of dexterity,

dysarthria, and oscillopsia associated with nystagmus appear. The disorder usually leaves patients incapacitated. Subtle motor system or cognitive dysfunction may be present. Imaging may show diffuse cerebellar atrophy, but contrast-enhancing lesions or lesions with mass effect are not part of PCD. CSF testing usually shows a lymphocytic pleocytosis and mildly elevated protein concentration during the early phase of the disorder, and oligoclonal bands have been reported.The PCD renders patients unable to walk, and dysarthria is frequently severe. Once the disorder reaches this stage, treatment with immunosuppression or effective treatment of the underlying malignancy rarely produces significant improvement. Patients with PCD and Hodgkin's lymphoma are predominantly male and younger than the females. The disorder frequently develops in patients who have already been treated for Hodgkin's lymphoma. This type of PCD also seems to be molecularly heterogeneous. PCD associated with Hodgkin's lymphoma appears to have a better prognosis for recovery. Spontaneous improvement was seen in 15% of cases in one series, and one patient improved significantly with effective treatment of Hodgkin's lymphoma.

Encephalomyelitis

- **Main causal cancers:** ---
- **Causal mechanism:** inflammation of the brain and spinal cord

Paraneoplastic encephalomyelitis (PEM) is a multifocal inflammatory disorder of the central nervous system (CNS) associated with remote neoplasia. Frequently, the disorder is accompanied by subacute sensory neuronopathy (SSN) due to involvement of the dorsal root ganglia. Although various malignancies have been reported in PEM, 80% of cases are associated with bronchial cancer, typically small cell lung carcinoma. Neurologic manifestations commonly precede the diagnosis of cancer, although variable presentations have been reported. Symptoms usually progress over the course of weeks to months, reaching a plateau of neurologic disability. Neurologic impairment may be more debilitating than the associated cancer. No effective therapeutic approaches have been established, although immunosuppressive therapies are commonly used.

Neurologic dysfunction probably results from an autoimmune reaction directed against onconeural antigens in the human nervous system. Polyclonal immunoglobulin G (IgG) anti-Hu antibodies or type 1 antineuronal nuclear antibodies are most prevalent (~50%), although several other circulating autoantibodies have been identified. Some patients have no identifiable paraneoplastic antibodies. These markers of paraneoplasia have an undetermined pathogenic role. Cytotoxic T cell–mediated neuronal damage is suspected, although no animal models have been developed to confirm this.

Almost all cases of PEM with anti-Hu antibodies are related to small-cell lung carcinoma. These antibodies react with a group of 35- to 40-kilodalton neuronal RNA-binding proteins, including HuD , PLE21/HuC, and Hel-N1. Nuclear and cytoplasmic staining of CNS neurons demonstrates the presence of these antibodies. A ubiquitous protein, HuR, is also an antigenic target. The neuronal proteins are homologous to the embryonic lethal abnormal visual (ELAV) protein in Drosophila species. Anti-Hu antibodies may alter the production of these proteins, which are essential for the development, maturation, and maintenance of the vertebrate nervous system. Intrathecal synthesis of anti-Hu antibodies may represent an autoimmune cross-reaction with neurologic tissue, triggered by a remote carcinoma. Recent work has focused on the detection of neuron-specific ELAV mRNA in peripheral blood of SCLC patients using real-time quantitative polymerase chain reaction (PCR).

In a recent report, a subset of patients with limbic encephalitis associated with a systemic neoplasm previously attributed to antibodies against voltage gated potassium channel antibodies actually recognize LGI1 protein complex epitopes and do not represent a channelopathy. The authors propose the term limbic encephalitis associated with LGI1 antibodies.

Other PEM antibodies include anti-CV2, anti-Yo, anti-Ma1, anti-Ta or anti-Ma2, anti-LGI1, and several other atypical antibodies. The targets of such antibodies may be quite varied, including neuropil and intraneuronal sites.

Nonneuronal autoantibodies, such as antinuclear antibodies and anticytoplasmic antibodies, are frequently detected in cases with anti-Hu antibodies or anti-Yo

antibodies. The presence of such nonneuronal autoantibodies, however, does not correlate with particular clinical characteristics.

Voltage-gated potassium channel antibodies may be associated with nonparaneoplastic limbic encephalitis.

Recent reports have noted detection of the prion-related protein and of herpes simplex virus by PCR in the cerebrospinal fluid (CSF) of patients with PEM. The significance of these findings is unclear.

Limbic Encephalitis

- **Main causal cancers:** small-cell lung carcinoma
- **Causal mechanism:** ---

The clinical, radiologic, and immunobiologic features of limbic encephalitis (LE) were described in two analyses encompassing 250 patients. LE may be mistaken for herpes simplex encephalitis because it presents with memory disturbance, agitation, and seizures. Magnetic resonance imaging (MRI) may show mesial temporal contrast enhancement or T2 signal hyperintensities. Fluorodeoxyglucose positron emission tomography (FDG-PET) may show hypermetabolism in the affected temporal lobes. The CSF shows increased protein concentration and a lymphocytic pleocytosis. Symptoms of SSN or involvement of brainstem or spinal cord may be present. Biopsy of temporal lobe may show perivascular lymphocytic infiltrates.

Molecular characterization of target antigens divides this syndrome into distinguishable diseases. Most cases of LE are associated with SCLC, and anti-Hu antibodies are present in serum and CSF. Patients with testicular cancer and LE harbor a different antibody. In a series of 13 patients with testicular cancer and LE, 10 harbored antibodies against a novel onconeural antigen named Ma2. Ma2 is a 40-kD protein not found in normal testis, but expressed in the normal human CNS and dorsal root ganglia. Two other onconeural antigens, ANNA-3 and PCA2, have been reported in patients with encephalomyelitis and SCLC. A related onconeural antigen, Ma1, normally found in the testis, is associated with cerebellar or brainstem dysfunction in patients with lung, breast, parotid gland, or colon cancer.

Breast cancer is the underlying malignancy in perhaps 5% of cases; anti-Ri antibodies have been reported in this setting. A patient with thymoma and a novel autoantibody directed against synaptic vesicles has been reported. LE has also been reported with Hodgkin's and non-Hodgkin's lymphoma.

LE may be one of the more treatable forms of central nervous system paraneoplastic disorder. More than 40% of patients followed for longer than 8 months in one series had some neurological improvement. Treatment of the underlying tumor seems more effective than immunosuppression. The distinction between anti-Ma2 and anti-Hu-associated LE is important clinically, because anti-Ma2 associated LE appears to have a better prognosis. Orchiectomy and aggressive treatment of residual disease appear to be the most effective treatment for anti-Ma2 associated LE. Immunosuppression has been less successful, but one patient improved after treatment with corticosteroids and intravenous IgG.

More recently, immunosuppression responsive forms of LE have been identified in association with anti voltage-gated potassium channels, and less well characterized antineuropil antibodies. MRI and FDG-PET demonstrated abnormalities on T2 and fluid-attenuated inversion recovery sequences, some patients also had diffusion abnormalities, as well as hypermetabolic regions on PET. In some patients clinical improvement with immunosuppression and/or successful ablation of the tumor was associated with improvement in PET and MRI abnormalities. LE appearing in a young female should prompt search for an associated ovarian teratoma.

Antibodies to voltage-gated potassium channels have been reported in patients with a syndrome similar to paraneoplastic LE, but usually without identifiable cancer. This syndrome appears to have a more favorable prognosis and response to immunosuppression. Rarely, small cell cancers of other organs, including the prostate, have been found as the only systemic cancer in patients with LE and anti-Hu antibodies.

Brainstem encephalitis and myelitis usually occur together and in association with LE. MRI scanning must exclude metastatic tumor. Most cases are associated with anti-Hu antibodies, but other autoantibodies may be present. Brainstem encephalitis and myelitis are usually rapidly and relentlessly progressive.

Paraneoplastic Opsoclonus (involving eye movement) - Myoclonus

- **Main causal cancers:** breast carcinoma, ovarian carcinoma, small-cell lung carcinoma, neuroblastoma (in children)
- **Causal mechanism:** Autoimmune reaction against the RNA-binding protein Nova-1

Opsoclonus Myoclonus Syndrome (OMS) is a rare neurological disorder of unknown causes which appears to be the result of an autoimmune process involving the nervous system. It is an extremely rare condition, affecting as few as 1 in 10,000,000 people per year. It affects 2 to 3% of children with neuroblastoma.

About half of all cases are associated with neuroblastoma and most of the others are suspected to be associated with a low-grade neuroblastoma that spontaneously regressed before detection. It is one of the few paraneoplastic (meaning 'indirectly caused by cancer') syndromes that occur in both children and adults, although the mechanism of immune dysfunction underlying the adult syndrome is probably quite different.

It is hypothesized that a viral infection (perhaps St. Louis encephalitis, Epstein-Barr, Coxsackie B, or enterovirus) causes the remaining cases, though a direct connection has not been proven.

OMS is not generally considered an infectious disease. OMS is not passed on genetically...

Anti-NMDA receptor encephalitis

- **Main causal cancers:** teratomas
- **Causal mechanism:** autoimmune reaction against NMDA-receptor subunits

It is an acute form of encephalitis, potentially lethal but with high probability for recovery, caused by autoimmune reaction against subunits of the glutamate NMDA receptor (is the predominant molecular device for controlling synaptic plasticity and memory function). The disease is associated with tumors, mostly teratomas of

the ovaries, and thus is considered a paraneoplastic syndrome. Howerever, there are a substantial number of cases with no detectable cancerous tissue.

Polymyositis

- **Main causal cancers**: Squamous Cell Carcinoma of the Lung, Thymic Carcinoma
- **Causal mechanism**: ---

It is a type of chronic inflammation of the muscles (inflammatory myopathy) related to dermatomyositis and inclusion body myositis. The etiology of polymyositis is unknown and may be multifactorial, perhaps related to autoimmune factors, genetics, and viruses. In rare cases, the cause is known to be infectious, associated with the pathogens that cause Lyme disease, toxoplasmosis, and other infectious agents. Polymyositis usually is considered non-fatal in the absence of ILD.

It is hypothesized that an initial injury causes release of muscle auto antigen, which is subsequently taken up by macrophages and presented to CD4+ TH cells. Activated TH cells synthesize IFN-γ that stimulate further macrophages and further inflammatory mediator release like IL-1 and TNF-α

Another important event in the pathogenesis of Polymyositis is the increased expression of MHC proteins by m/s cells. Auto-Ag is presented in association with MHC-I molecules on the surface of Myocytes and is recognized by CD8 cytotoxic T cells that subsequently initiate m/s destruction.

Non-neurologic Paraneoplastic Syndromes:

1) Endocrinopathies:

Cushing syndrome

- **Main causal cancers:** Small-cell lung cancerm, Pancreatic carcinoma, Neural tumors, Thymoma
- **Causal mechanism:** Ectopic ACTH and ACTH-like substance

First described by Brown in 1928, the syndrome of ectopic adrenocorticotropic hormone syndrome (ACTH) was further characterized in 1965 in 88 patients with Cushing's syndrome and cancer. This report was the first to suggest that tumors produced ACTH or an ACTH-like substance that led to adrenal hyperplasia and hypercortisolism, and thus the term ectopic ACTH production was coined. Subsequently, the gene responsible, the proopiomelanocortin gene, was cloned. Poopiomelanocortin contains not only ACTH, but melanocyte-stimulating hormone, lipotropin, endorphins, and enkephalins. Tumors express proopiomelanocortin in different ways in small cell lung cancers (SCLCs), for example, release a higher level of ACTH precursors in the circulation, whereas carcinoid tumors produce intact ACTH in large amounts. Ectopic ACTH production is commonly associated with SCLC but can also be found in a variety of neoplasms. Although 3% to 7% of patients with SCLC develop Cushing's syndrome, many patients with SCLC secrete ACTH precursors without developing the syndrome.

The differential diagnosis of a patient with hypercortisolism includes Cushing's disease, adrenal dysfunction, ectopic ACTH production, and corticotropin-releasing hormone (CRH) overproduction. Pituitary overproduction (Cushing's disease) is the cause of disease in over 55% of patients, followed in frequency by adrenal dysfunction, ectopic ACTH production (occurring in 11% to 25%), and CRH overproduction, which is quite rare. Signs and symptoms of classic hypercortisolism include truncal obesity, purple striae, hypertension, fatigue, moon facies, buffalo hump, weakness, depression, amenorrhea, hirsutism, decreased libido, osteopenia, osteoporosis, impaired wound healing, impaired glucose

tolerance diabetes, easy bruising, and edema. In contrast, ectopic ACTH production from SCLC causes myopathy with weakness, muscle wasting, weight loss, hyperpigmentation, and hypokalemia. Carcinoid tumors that secrete ectopic ACTH may cause signs and symptoms that overlap those of pituitary-dependent Cushing's disease and paraneoplastic ACTH overproduction.

Syndrome of inappropriate antidiuretic hormone (SIADH)

- **Main causal cancers:** small-cell lung cancer, CNS malignancies
- **Causal mechanism:** antidiuretic hormone

The syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) is characterized by excessive release of antidiuretic hormone (ADH or vasopressin) from the posterior pituitary gland or another source. The result is hyponatremia and sometimes fluid overload. It is usually found in patients diagnosed with small-cell carcinoma of the lung, pneumonia, brain tumors, head trauma, strokes, meningitis, and encephalitis.

The normal function of ADH on the kidneys is to control the amount of water reabsorbed by kidney nephrons. ADH acts in the distal portion of the renal tubule (Distal Convoluted Tubule) as well as on the collecting duct and causes the retention of water, but not solute. Hence, ADH activity effectively dilutes the blood (decreasing the concentrations of solutes such as sodium).

ADH is secreted to prevent water loss in the kidneys. When water is ingested, it is taken up into the circulation and results in a dilution of the plasma. This dilution, otherwise described as a reduction in plasma osmolality, is detected by osmoreceptors in the hypothalamus of the brain and these then switch off the release of ADH. The decreasing concentration of ADH effectively inhibits the aquaporins in the collecting ducts and distal convoluted tubules in the nephrons of the kidney. Hence, less water is reabsorbed, thereby increasing urine output, decreasing urine osmolality, and normalizing blood osmolality. In SIADH the release of ADH is not inhibited by a reduction in plasma osmolality when the individual ingests water and the osmolality of the plasma drops. As the main solute of plasma is sodium, this hypoosmolar state is usually detected as a low sodium

level on laboratory testing. SIADH is therefore primarily a condition that results in the abnormal handling of water loading and not a problem with excessive solute loss. This is why it is usually treated with fluid (in particular water) restriction. Diuretics may also be given to decrease reabsorption of water, but care must be taken not to correct water imbalances too rapidly.

This causes dilutional hyponatremia and all the consequences associated with that condition: headache, nausea, vomiting, and confusion may ensue. Severe hyponatremia may cause convulsions or coma.

The abnormalities underlying type D syndrome of inappropriate antidiuretic hormone hypersecretion concern individuals where vasopressin release and response are normal but where abnormal renal expression and translocation of aquaporin 2, or both are found. It has been suggested that this is due to abnormalities in the secretion of secretin in the brain and that "Secretin as a neurosecretory hormone from the posterior pituitary, therefore, could be the long-sought vasopressin independent mechanism to solve the riddle that has puzzled clinicians and physiologists for decades."

Hypercalcemia

- **Main causal cancers:** Lung cancer (typically squamous cell), Breast carcinoma, Renal carcinoma, Multiple myeloma (may occur independent of osteolytic lesions), Adult T cell leukemia/lymphoma, Ovarian carcinoma
- **Causal mechanism:** PTHrP (Parathyroid hormone-related protein), TGF-α, TNF, IL-1

Tumors associated with bone metastases such as breast, prostate, and lung cancers can lead to hypocalcemia. Patients with hypocalcemia and osteoblastic metastases have increased skeletal avidity for calcium, thus implicating the rapid deposition of calcium in bone as the cause of hypocalcemia. Contributing factors associated with hypocalcemia include vitamin D deficiency associated with the malignant state, severe hypomagnesemia due to paraneoplastic renal loss of magnesium, and parathyroid hormone imbalance. Hypocalcemia can also occur in patients whose

tumors secrete calcitonin (i.e., medullary carcinoma of the thyroid and, rarely, breast cancer, colorectal cancer, SCLC, and carcinoid).

Hypocalcemia can have a wide variety of clinical manifestations. In many cases it is asymptomatic; however, it can occasionally lead to the development of significant symptoms secondary to neuromuscular irritability and cardiovascular changes. These symptoms include peripheral and perioral paraesthesia, cramps, tetany, seizures, bronchospasm, laryngospasm, anxiety, confusion, cardiac arrhythmias, and congestive cardiac failure. In severe cases, hypocalcemia can be life threatening, especially if it remains unrecognized and untreated.

Following the diagnosis of malignancy-related hypocalcemia, rapid correction of serum calcium with appropriate replacement therapy is paramount. The requirement for intravenous versus oral calcium replacement therapy depends on the severity of hypocalcemia and the clinical manifestations of the disease. In the presence of hypomagnesemia, repletion of serum magnesium levels is essential to prevent a state of functional hypoparathyroidism and enable correction of serum calcium. Finally, if vitamin D deficiency is confirmed, supplementation is necessary to allow further restoration of calcium-phosphate balance. Chemotherapy, through direct activity on osteoblastic metastases, has a role in the management of malignancy-related hypocalcemia and should be considered in refractory cases.

Hypoglycemia

- **Main causal cancers:** Fibrosarcoma, Other mesenchymal sarcomas, Hepatocellular carcinoma
- **Causal mechanism:** Insulin or insulin-like substance or "big" IGF-II

Hypoglycemia is an abnormally diminished content of glucose in the blood. It can produce a variety of symptoms and effects but the principal problems arise from an inadequate supply of glucose to the brain, resulting in impairment of function (neuroglycopenia). Effects can range from mild dysphoria to more serious issues such as seizures, unconsciousness, and (rarely) permanent brain damage or death.

The most common forms of hypoglycemia occur as a complication of treatment of diabetes mellitus with insulin or oral medications. Hypoglycemia is less common in non-diabetic persons, but can occur at any age. Among the causes are excessive insulin produced in the body (hyperinsulinemia), inborn errors of metabolism, medications and poisons, alcohol, hormone deficiencies, prolonged starvation, alterations of metabolism associated with infection, and organ failure.

Nonpancreatic tumors may cause recurrent hypoglycemia known as nonislet cell tumor hypoglycemia. It is due to overproduction and secretion by the tumor of incompletely processed IGF-II, termed big IGF-II. We recently identified a patient with recurrent hypoglycemia and low insulin, but without elevated big IGF-II. Multiple small lung nodules were detected by computed tomography scan. An undifferentiated large-cell carcinoma was diagnosed from an axillary lymph node metastasis.

Carcinoid syndrome

- **Main causal cancers:** Bronchial adenoma (carcinoid type), pancreatic carcinoma, Gastric carcinoma
- **Causal mechanism:** Serotonin, bradykinin

Carcinoid syndrome refers to the array of symptoms that occur secondary to carcinoid tumors. The syndrome includes flushing and diarrhea, and, less frequently, heart failure and bronchoconstriction. It is caused by endogenous secretion of mainly serotonin and kallikrein.

Carcinoid tumors produce the vasoactive substance, serotonin. It is commonly, but incorrectly, thought that serotonin is the cause of the flushing. The flushing results from secretion of kallikrein, the enzyme that catalyzes the conversion of kininogen to lysyl-bradykinin. The latter is further converted to bradykinin, one of the most powerful vasodilators known. Other components of the carcinoid syndrome are diarrhea (probably caused by serotonin), a pellagra-like syndrome (probably caused by diversion of large amounts of tryptophan from synthesis of the vitamin B3, niacin, to the synthesis of 5-hydroxyindoles including serotonin), fibrotic lesions of the endocardium, particularly on the right side of the heart resulting in

insufficiency of the tricuspid valve and, less frequently, the pulmonary valve and, uncommonly, bronchoconstriction. The pathogenesis of the cardiac lesions and the bronchoconstriction is unknown, but the former probably involves activation of serotonin 5-HT2B receptors by serotonin. When the primary tumor is in the gastrointestinal tract, as it is in the great majority of cases, the serotonin and kallikrein are inactivated in the liver; manifestations of carcinoid syndrome do not occur until there are metastases to the liver or when the cancer is accompanied by liver failure (cirrhosis). Carcinoid tumors arising in the bronchi may be associated with manifestations of carcinoid syndrome without liver metastases because their biologically active products reach the systemic circulation before passing through the liver and being metabolized.

In most patients, there is an increased urinary excretion of 5-HIAA (5-hydroxyindoleacetic acid), a degradation product of serotonin.

2) Hematological

Granulocytosis

- **Main causal cancers**: lymphoma
- **Causal mechanism:** G-CSF

Granulocytosis with elevation of the white blood cell count above $15x10^9/L$ without infection or leukemia is common in neoplasms. Neoplasms most commonly associated with granulocytosis include Hodgkin's lymphoma, lymphoma, and a variety of solid tumors, including gastric, lung, pancreatic, and brain cancers and malignant melanoma. Paraneoplastic granulocytosis consists of mature neutrophils, in contrast to chronic myelogenous leukemia, in which more immature forms are seen, along with basophils and eosinophils, a decreased leukocyte alkaline phosphatase level, elevated vitamin B_{12} level and vitamin B_{12} binding capacity, and the presence of the Philadelphia chromosome. The common mechanism associated with tumor-associated granulocytosis is tumor production of growth factors.

Polycythemia

- **Main causal cancers:** Renal carcinoma, Cerebellar hemangioma, Hepatocellular carcinoma
- **Causal mechanism:** Erythropoietin

The von Hippel-Lindau (VHL) tumor suppressor gene targets hypoxia-inducible transcription factors (HIFs) for proteasomal degradation. Erythrocytosis due to inappropriate production of erythropoietin (EPO), one of the HIF target genes, is a classic albeit rare finding in patients with renal cancer. We report the clinical to molecular analysis in a patient in whom a thrombotic myocardial infarction was the first manifestation of a clear cell renal carcinoma associated with an elevated serum EPO level (109 U/L) and erythrocytosis (hemoglobin 200 g/L [20 g/dL]). The tumor strongly expressed EPO messenger RNA and the 2 regulatory subunits HIF-1α and HIF-2α. Sequence analysis of tumor tissue identified a point mutation of the VHL gene (nucleotide 701 T>C) with a predicted amino acid exchange (Leu163Pro). This structural change, although located at distance to the HIF-binding region, was found to inhibit binding of HIF-1α to VHL, thus leading to accumulation of HIF, which drives EPO production.

Erythropoietin (EPO) production in liver and kidneys is inversely related to oxygen availability, thus establishing a negative feedback control of erythropoiesis.1 Studies of EPO regulation led to the identification of the transcription factor hypoxia-inducible factor (HIF). HIF is composed of an HIFα and HIFβ subunit and binds to hypoxia response elements located in the vicinity of the EPO gene and several other genes induced by hypoxia. HIFα is the oxygen-regulated component, and 2 subunits with marked sequence homology have been described: HIF-1α and HIF-2α. In the presence of oxygen, HIFα is rapidly degraded by cellular proteasomes. The protein targeting HIFα for proteasomal degradation is the von Hippel-Lindau (VHL) protein, a tumor suppressor protein that is mutated in the germ line of patients affected by the VHL disease. Recent work has shown that oxygen-dependent hydroxylation of two proline residues of HIFα (Pro 402 and 564) essential for binding of HIF to pVHL and represent a critical component of the oxygen-sensing mechanism.

Certain tumors that are associated with an inappropriate increase in EPO production can lead to erythrocytosis. Renal cancer is the most frequent cause of paraneoplastic polycythemia, and EPO expression has been demonstrated at the protein and messenger RNA (mRNA) level in renal tumors and tumor-derived primary cell lines. However, the mechanisms activating the EPO gene in association with malignant transformation have not been clarified.

Trousseau sign

- **Main causal cancers:** Pancreatic carcinoma, Bronchogenic carcinoma
- **Causal mechanism:** Mucins that activate clotting, others

The Trousseau sign of malignancy is a medical sign found in certain cancers that is associated with venous thrombosis and hypercoagulability. It is also referred to as Trousseau syndrome and is distinct from the Trousseau sign of latent tetany.

Some malignancies, especially adenocarcinomas of the pancreas and lung, are associated with hypercoagulability (the tendency to form blood clots) for reasons that are incompletely understood, but may be related to factors secreted by the tumors, in particular a circulating pool of cell-derived tissue factor-containing microvesicles.

In patients with malignancy-associated hypercoagulable states, the blood may spontaneously form clots in the portal vessels, the deep veins of the extremities (such as the leg), or the superficial veins anywhere on the body. These clots present as visibly swollen blood vessels (vasculitis), especially the veins, or as intermittent pain in the affected areas. The pathological phenomenon of clots forming, resolving and then appearing again elsewhere in the body has been named thrombophlebitis migrans or migratory thrombophlebitis.

Nonbacterial thrombotic endocarditis

- **Main causal cancers:** Advanced cancers
- **Causal mechanism:** Hypercoagulability

Nonbacterial thrombotic endocarditis may lead to thrombotic or hemorrhagic complications and may occur with or without DIC. It is characterized by sterile, verrucous fibrin-platelet lesions on the heart valves. Although nonbacterial thrombotic endocarditis most commonly affects the aortic and mitral valves, any cardiac valve may be affected; vegetations on the atrioventricular valves are present on the atrial surface, while those involving the semilunar valves are found on the ventricular surface of the valve. Although the pathogenesis of nonbacterial thrombotic endocarditis is not fully understood, the most important predisposing factors appear to be an underlying coagulopathy (usually disseminated intravascular coagulation), microscopic edema, degeneration of valvular collagen, and perhaps a local valvular effect of mucin-producing carcinomas.

The diagnosis of nonbacterial thrombotic endocarditis is not easily made and is considerably more elusive than that of bacterial endocarditis. Not only is the marker of bloodstream infection lacking, but the small friable vegetations frequently embolize, leaving only small remnants to be identified on the valve. Indeed, cardiac murmurs, a hallmark of bacterial endocarditis, are frequently absent, and echocardiography is less sensitive for the detection of nonbacterial thrombotic endocarditis than it is for bacterial endocarditis. Nonbacterial endocarditis should be suspected in cancer patients who present with ischemic embolic events and is most commonly seen with adenocarcinomas of the lung and pancreas.

Treatment of the underlying malignancy is the primary therapy. Anticoagulation therapy should be withheld from patients with disseminated cancer when there is no hope of tumor regression; in most instances, a diagnosis of nonbacterial thrombotic endocarditis or a strong suspicion of this diagnosis warrants anticoagulation therapy.

Anemia

- **Main causal cancers:** Thymic neoplasms
- **Causal mechanism:** Unknown

The most common anemias in cancer patients are normocytic normochromic/hypochronic anemia of chronic disease, anemia secondary to bone marrow invasion (often associated with leukoerythroblastosis), and anemia secondary to chemotherapy and radiation treatment. Normochromic, normocytic anemia of cancer is a common paraneoplastic syndrome, characterized by low serum iron levels, normal or increased ferritin levels, normal iron stores, and a low serum erythropoietin level.

A rare cause of anemia in cancer patients is pure red cell aplasia. One well-described paraneoplastic syndrome is that of thymoma and pure red cell aplasia with associated hypogammaglobulinemia. Pure red cell aplasia may also be associated with a variety of lymphoid malignancies, including chronic lymphocytic leukemia (CLL) and large granular lymphocytic lymphoma and leukemia. Rarely, pure red cell aplasia is associated with solid tumors.

Autoimmune hemolytic anemias are typically associated with B-cell malignancies, including CLL and lymphomas, and arise secondary to immunoregulatory abnormalities in these diseases, rather than to a direct secretion of tumor-derived substances. Hallmarks of the disease are a positive direct antiglobulin test result, elevated reticulocyte count, decreased haptoglobin level, and elevated lactate dehydrogenase level. Warm antibody hemolytic anemia is most commonly associated with lymphomas, CLL, and mucin-producing adenocarcinomas. Cold agglutinin disease is most common in Waldenström's macroglobulinemia and lymphomas. Autoimmune hemolytic anemia is rarely associated with solid tumors; however, an association with ovarian, GI, lung, breast, and renal cell cancers has been reported. Corticosteroid treatment appears to be less effective in autoimmune hemolytic anemia associated with carcinomas than in those that are idiopathic or associated with lymphoid malignancies. The Coombs test result may revert to negative with control of the tumor.

Microangiopathic hemolytic anemia is characterized by fragmentation of red cells, and although often observed in thrombotic thrombocytopenic purpura and the

hemolytic-uremic syndrome, it has also been reported in association with malignancy. Disseminated intravascular coagulation (DIC) may contribute to microangiopathic hemolytic anemia in metastatic carcinomas by inducing the red cell fragmentation from fibrin strands. Patients typically have pronounced schistocytosis with microspherocytes, spherocyte-shaped erythrocytes smaller than 5 mcm in diameter. The reticulocyte count is typically increased, and a leukoerythroblastic blood picture may predominate. Microangiopathic hemolytic anemia is typically associated with adenocarcinoma of the GI tract, heart, lung, and prostate. The mechanism remains unknown. Microangiopathic hemolytic anemia syndrome may respond to effective anticancer therapy.

3) Mucocutaneous

Acanthosis nigricans

- **Main causal cancers:** Gastric carcinoma, Lung carcinoma, uterine carcinoma
- **Causal mechanism:** Immunologic, secretion of EGF

Acanthosis nigricans is characterized by gray-brown hyperpigmented, velvety plaques that often affect the neck, flexor areas, and anogenital region. The malignant and benign forms are similar in appearance, but the malignant form progresses rapidly, and pruritus is common. The malignant variety may precede the tumor, occur simultaneously, or follow the appearance of the tumor. It is typically associated with adenocarcinomas of the GI tract, predominantly gastric cancer, but has also been associated with a variety of other adenocarcinomas, including lung, breast, ovarian, and even hematologic malignancies. The pathogenesis remains uncertain, but appears to be link to overproduction of transforming growth factor by the tumor. Tripe palms are often associated with acanthosis nigricans. Patients show thickened palms with exaggerated hyperkeratotic ridges, a velvety texture, and brown hyperpigmentation. Tripe palms usually occur in patients with lung and gastric cancers.

Dermatomyositis

- **Main causal cancers:** Bronchogenic carcinoma, Breast carcinoma
- **Causal mechanism:** Immunologic

Although most patients with dermatomyositis do not have cancer, patients with the disorder do seem to be at higher risk for discovery of a cancer. Breast cancer is the most commonly associated cancer in women, and lung and GI cancer in men. Association with tumors of the pancreas, melanoma, germ cell tumors, nasopharyngeal carcinoma, and lymphoma has also been reported.

Immunosuppressive treatments effective in idiopathic dermatomyositis seem effective in the paraneoplastic disorder. It is unclear if antineoplastic therapy leads to improvement in the muscle disease in the absence of concomitant immunosuppression.

Necrotizing myopathy is characterized by rapidly progressive, predominantly proximal weakness and marked pain and tenderness of the muscles. SCLC, breast cancer, and GI cancers have been reported with necrotizing myopathy. Although biopsy usually shows necrotic fibers without inflammatory infiltrates, immunosuppression has benefited some patients with this disorder.

Dermatomyositis may be idiopathic or paraneoplastic and has been linked to malignancy in over 25% of cases. Clinical signs of dermatomyositis include a heliotrope rash of the periorbital skin, shawl sign, V-neck erythema, periungual telangiectasia and erythema, and Gottron's sign (pathognomonic erythematous papules on the extensor surfaces of joints). Patients also exhibit progressive proximal muscle weakness. Dermatomyositis most commonly is associated with cancers of reproductive organs in women and respiratory tract in both sexes. Malignancy can precede, follow, or occur simultaneously with dermatomyositis; the most frequent pattern is onset of cancer within 1 year of the diagnosis of dermatomyositis.

Other collagen-vascular disorders such as systemic lupus erythematosus may be rarely associated with leukemias or lymphomas. Pemphigus erythematosus is associated with thymoma and myasthenia gravis.

Leser-Trélat sign

- **Main causal cancers:** stomach adenocarcinoma, lymphoma, squamous cell carcinoma, breast and colon cancer
- **Causal mechanism:** Probably inflammatory reaction

It refers to the sudden appearance of seborrheic keratoses secondary to an occult malignancy and often with an inflammatory base. This can be an ominous sign of internal malignancy as part of a paraneoplastic syndrome. In addition to the development of new lesions, preexisting ones frequently increase in size and become symptomatic.

Necrolytic migratory erythema

- **Main causal cancers:** Glucagonoma
- **Causal mechanism**: ---

Necrolytic migratory erythema is solely associated with glucagonoma and is characterized by erythema, papules, vesicles, and pustules that progress to blistering and epidermal necrosis on the central face, lower abdomen, perineum, and buttocks and other areas. The eruption clears after resection of the tumor, but in metastatic glucagonoma may wax and wane. Somatostatin is beneficial due to its suppression of glucagon secretion.

Sweet's syndrome

- **Main causal cancers**: leukemia
- **Causal mechanism**: ---

Sweet's syndrome (SS), or acute febrile neutrophilic dermatosis is a skin disease characterized by the sudden onset of fever, leukocytosis, and tender, erythematous, well-demarcated papules and plaques which show dense infiltrates by neutrophil granulocytes on histologic examination.

The syndrome was first described in 1964 by Dr Robert Douglas Sweet. It was also known as Gomm-Button disease in honour of the first two patients Dr Sweet diagnosed with the condition.

Although it may occur in the absence of other known disease, SS is often associated with hematologic disease (including leukemia), and immunologic disease (rheumatoid arthritis, inflammatory bowel disease).

A genetic association has been suggested, but no specific genetic link has been identified.

Florid cutaneous papillomatosis

- **Main causal cancers**: breast, bladder, hepatobiliary cancer and gastric adenocarcinoma
- **Causal mechanism**: ---

Florid cutaneous papillomatosis (also known as Schwartz-Burgess syndrome and FCP) is the sudden onset of numerous cutaneous papillomas that are indistinguishable from viral warts, and associated with underlying malignancy.

Florid cutaneous papillomatosis presents with verrucous papulonodules resembling viral warts. These skin lesions develop on the trunk, extremities, and face, and are almost twice as common in men than in women, especially individuals aged 53-72 years. This papillomatosis may also present with other cutaneous signs of internal malignancy, such as acanthosis nigricans type I and Leser-Trélat.

Florid cutaneous papillomatosis is associated with underlying malignancy, most often gastric adenocarcinoma but also with breast cancer, bladder cancer, hepatobiliary cancer, ovarian cancer, uterine cancer, prostate cancer[citation needed], and lung cancer; however, the cause of FCP is currently not known.

Pyoderma gangrenosum

- **Main causal cancers:** Myelocytic leukemia, Hairy cell leukemia
- **Causal mechanism:** Probably immunologic

It is a disease that causes tissue to become necrotic, causing deep ulcers that usually occur on the legs. The lesions of pyoderma gangrenosum appear as painful papules that subsequently ulcerate and form nonhealing ulcers with violaceous irregular borders and a purulent, hemorrhagic exudate with a necrotic base. Histopathologic examination demonstrates a neutrophilic infiltrate. Pyoderma gangrenosum is associated with hematological malignancies, including cutaneous T-cell lymphomas, as well as gastric carcinoma and other GI abnormalities.

Acquired generalized hypertrichosis

- **Main causal cancers**: ---
- **Causal mechanism**: ---

Hypertrichosis (also called Ambras Syndrome) is an abnormal amount of hair growth on the body; extensive cases of hypertrichosis have informally been called werewolf syndrome. There are two distinct types of hypertrichosis: generalized hypertrichosis, which occurs over the entire body, and localized hypertrichosis, which is restricted to a certain area. Hypertrichosis can be either congenital (present at birth) or acquired later in life. The excess growth of hair occurs in areas of the skin with the exception of androgen-dependent hair of the pubic area, face, and axillary regions.

Several circus sideshow performers in the 19th and early 20th centuries, such as Julia Pastrana, had hypertrichosis. Many of them worked as freaks and were promoted as having distinct human and animal traits.

4) Others

Membranous glomerulonephritis

- **Main causal cancers:** solid tumors of the lung and colon, hematological malignancies
- **Causal mechanism:** Tumor antigens, Immune complexes

Membranous glomerulonephritis (MGN) is a slowly progressive disease of the kidney affecting mostly patients between ages of 30 and 50 years, usually Caucasian.

It is one of the more common forms of nephrotic syndrome.

MGN is caused by circulating immune complex. The immune complexes are formed by binding of antibodies to antigens in the glomerular basement membrane. The antigens may be part of the basement membrane, or deposited from elsewhere by the systemic circulation.

The immune complex serves as an activator that triggers a response from the C5b - C9 complements, which form a membrane attack complex (MAC) on the glomerular epithelial cells. This, in turn, stimulates release of proteases and oxidants by the mesangial and epithelial cells, damaging the capillary walls and causing them to become "leaky". In addition, the epithelial cells also seem to secrete an unknown mediator that reduces nephrin synthesis and distribution.

Tumor-induced osteomalacia

- **Main causal cancers:** Hemangiopericytoma, Phosphaturic mesenchymal tumor
- **Causal mechanism:** FGF-23 (Fibroblast growth factor-23)

Tumor-induced or oncogenous osteomalacia is a rare paraneoplastic syndrome characterized by osteomalacia with hypophosphatemia, hyperphosphaturia, and undetectable or inappropriately low circulating concentrations of 1,25-

dihydroxyvitamin D3. Mean age at diagnosis is approximately 35 years. Patients typically present with bone pain, phosphaturia, renal glycosuria, hypophosphatemia, normocalcemia with normal parathyroid hormone function, low levels of 1, 25-dihydroxyvitamin D3, and increased alkaline phosphatase levels. It is therefore important to monitor serum phosphate levels as well as to identify other biochemical features such as abnormally low circulating levels of 1,25(OH)2D3 and low phosphate reabsorption per liter of glomerular filtrate. The proposed mechanisms include inhibition of the conversion of 1,25-dihydroxyvitamin D3 and a tumor-secreted phosphaturic substance. The majority of neoplasms causing this syndrome are benign, but the syndrome has also been described with carcinoma of the lung, multiple myeloma, and prostate cancer. The typical tumor involves prominent giant cells, spindle cells, and a high degree of vascularity. Approximately half of the tumors are in the lower extremities, and the remaining tumors are divided between the head and neck and upper extremities, with some patients having tumors at multiple sites.

The definitive therapy is removal of the tumor, if possible, which leads to clinical and biochemical cure. Otherwise, treatment requires large doses of vitamin D and phosphate.

Stauffer syndrome

- **Main causal cancers**: renal cell carcinoma
- **Causal mechanism**: ---

This condition is a constellation of signs and symptoms of liver dysfunction that arise due to presence of renal cell carcinoma and, more rarely, in connection with other malignant neoplasms. The hepatic abnormalities are not due to tumor infiltration of the liver or intrinsic liver disease; they instead reflect the presence of a paraneoplastic syndrome.

Stauffer syndrome causes abnormal liver function tests, especially those that reflect the presence of cholestasis, i.e. abnormal bile flow. The symptoms and signs resolve if the renal cell carcinoma (or another associated tumor) is successfully ablated.

5) Fever

Neoplastic fever, a paraneoplastic syndrome caused by cancer itself, represents a diagnostic challenge for the clinician and is an important issue in supportive oncology. Timely recognition of this febrile condition by differentiating it from other cancer-associated fevers, such as infection and drug reaction, is essential for effective patient management. Although the pathophysiology of neoplastic fever is not well understood, it is suspected to be cytokine mediated. In clinical practice, when a patient with cancer presents with unexplained fever, extensive diagnostic studies are needed to differentiate neoplastic fever from nonneoplastic fever. Only after excluding identifiable etiologies of fever can the diagnosis of neoplastic fever be suspected. According to our experience, the naproxen test is a safe and useful test in differentiating neoplastic fever from infectious fever in patients with cancer. In addition, naproxen and other nonsteroidal anti-inflammatory drugs have been effective in the management of neoplastic fever and offer a significant palliative benefit for the patient.

References:

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3) The Cancer Dictionary, 3rd Edition
4) CURRENT's Medical Diagnosis and Treatment, 50th Edition
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6) Medscape (http://www.medscape.com)
7) PubMed (http://www.ncbi.nlm.nih.gov/pubmed)

Appendix I Paraneoplastic syndromes associated with cancer.

Hormone Excess or Syndrome	Non-Small Cell Lung Cancer	Small Cell Lung Cancer	Breast Cancer	Renal Cell Carcinoma	Adrenal Cancer	Hepato-cellular Carcinoma	Gastro-intestinal Cancers	Multiple Myeloma	Lymphoma	Thymoma	Prostatic Cancer	Ovarian Cancer	Chorio-carcinoma	Germ Cell Cancers
Endocrine														
Hypercalcemia	++		++	++	++			++	+		++			
Cushing syndrome	+	++		+	++					++	+			
SIADH	++	++												
Hypoglycemia					+	++	+							
Gonadotropin secretion	+	++		+	+	+	+						++	++
Hyperthyroidism													++	+
Hematologic														
Erythrocytosis				++	+	++								
Pure red cell aplasia									+	++				
Coagulopathy			++				++				++	+		
Thrombophlebitis			+				++				++	+		
Neurologic														
Lambert-Eaton myasthenia syndromes	+	++	+				+		+	+		+		
Subacute cerebellar syndrome		++	+				+		+			+		
Sensory motor peripheral neuropathy		++												
Stiff man syndrome			+											
Dermatologic														
Dermatomyositis	++	++	+				+					+		
Acanthosis nigricans	+		+				++				+			
Fever				++		++			++	+				
Hypertrophic osteoarthropathy	++													

+, reported associated; ++, strong association.
SIADH, syndrome of inappropriate antidiuretic hormone.

		ANTIBODIES AGAINST INTRACELLULAR ANTIGENS (all defined as "well characterised" except anti-Tr) PERCENTAGE OF ANTIBODY POSITIVE PARANEOPLASTIC PATIENTS WITH CLINICAL FEATURE						
	Name of onconeural antibody	**anti-Hu** (anti-neuronal nuclear antibody type 1)	**anti-Yo** (anti-Purkinje cell antibody type 1)	**anti-Ma2 +/- anti-Ma1** (anti Ma2 is also known as anti-Ta)	**anti-CV2/CRMP5** (anti-crossveinless-2 / collapsin response mediated protein 5)	**anti-Amphiphysin**	**anti-Ri** (anti-neuronal nuclear antibody type 2)	**anti-Tr** (anti-Purkinje cell antibody Tr)
	Predominant neoplastic type(s), (% of histologically proven malignancies in the study)	Small cell lung carcinoma (93%) (13% of which had co-existing tumour, most commonly renal-cell carcinoma)	Ovarian carcinoma (47%) breast carcinoma (25%), endometrial and tubal carcinoma (13%), adenocarcinoma unknown primary (11%)	Testicular carcinoma (55%), non-small cell lung carcinoma (21%)	Small cell lung carcinoma (77%), thymoma (8%)	Small cell lung carcinoma (59%), breast carcinoma (35%)	Breast carcinoma (43%), small cell lung carcinoma (24%), non-small cell lung carcinoma (24%)	Hodgkin's disease (100%)
Paraneoplastic syndrome	Limbic encephalitis	14%		71%	✓	6%		4%
	Paraneoplastic cerebellar degeneration	"Cerebellar syndrome" 18%	100%	Clinically predominant cerebellar ataxia 5%	"Cerebellar ataxia" 26%	"Cerebellar syndrome" 17%	50%	96%
	Subacute sensory neuronopathy	40%			27%	22%		
	Chronic gastrointestinal pseudoobstruction	✓			21%			
	Opsoclonus-myoclonus syndrome	1%	5%		5%	9%	36%	
	Lambert Eaton myasthenic syndrome	6%			9%	8%	4%	
	Brainstem encephalitis	✓		66%	5%		71%	
	Acquired peripheral nerve hyperexcitability syndrome				Neuromyotonia <1%	Neuromyotonia 3%		
	Stiff person syndrome					21% stiff limb 8% stiff person		
	Myasthenia gravis				3%			
Encephalomyelitis = multitude of levels of nervous system involved		✓		✓	✓	✓	✓	
Neurological manifestation	Seizures	✓		✓	9%	✓	Seizures 4%	
	Cognitive dysfunction & psychiatric symptoms	"Cognitive decline" in limbic encephalitis cohort 14%	"Cognitive impairment, usually emotional lability and memory deficit" 18%		Dementia 25%; personality change 9%; "confusion" 8%; depression 8%; psychosis 3%	Subacute delirium, cognitive dysfunction, psychiatric disorder, or confusion 30%	Confusion/encephalopathy 11%	
	Movement disorder		Extrapyramidal rigidity and tremor or dyskinesia 4%	Atypical Parkinsonism 8%	Chorea 11%		Parkinsonism 7% Chorea 4%	
	Myelopathy	2%		5%	16%	27%	18%	
	Peripheral neuropathy	Sensory 40% Mixed somatic 30% Motor 2%	Hyporeflexia or mild distal sensory complaints 47%		Sensory 27% Mixed 22% Motor 2%	Sensory 22% Sensorimotor 17% Motor 6 % Polyradiculopathy 3%	Sensorimotor, polyradiculopathy, small fibre neuropathy 25%	
	Autonomic dysfunction	18%			31%			
% of antibody positive patients with other clinical features		"Cranial neuropathy" 15%		Additional presence of anti-Ma1 (39% of patients) = higher chance of tumour other than testicular, worse prognosis, hypothalamic dysfunction and limbic encephalitis.	Abnormalities of olfaction and taste 14%, optic neuropathy 7%	"Cranial neuropathies" 9%, optic neuritis / retinitis 5%		
Reference		Lucchinetti (1998)[10], 162 patients (53M, 109F),	Peterson (1992)[11], 55 patients (all F)	Dalmau (2004)[16] 38 patients (26M, 12F)	Yu (2001)[17], 116 patients (49M, 67F)	Pittock (2005)[18], 63 patients (25M, 38F)	Pittock (2003)[19], 28 patients (10M, 18F)	Bemal (2003)[14], 28 patients (22M, 6F)

Classical paraneoplastic syndromes are shaded in blue. ✓ = case series documents manifestation but does not publish number of cases.

Appendix II

		ANTIBODIES AGAINST SURFACE ANTIGENS PERCENTAGE OF ANTIBODY POSITIVE PARANEOPLASTIC PATIENTS WITH CLINICAL FEATURE			
Name of onconeural antibody		anti-NMDA (anti-NR1-NR2 heteromer of the N-methyl-D-aspartic acid receptor)	anti-VGKC (anti-voltage gated potassium channel)	anti-VGCC (anti-P/Q type voltage gated calcium channel)	anti-AchR (anti-acetylcholine receptor)
Predominant neoplastic type(s), (% of histologically proven malignancies in the study)		Ovarian or other teratoma (94%)	Small cell lung carcinoma (21%), benign adenoma (21%), thymoma (17%), prostate adenocarcinoma (17%)	Small cell lung carcinoma (98%)	Thymoma (100%)
Paraneoplastic syndrome	Limbic encephalitis	✓	71%		<10%
	Paraneoplastic cerebellar degeneration		8%	16%	
	Subacute sensory neuronopathy				
	Chronic gastrointestinal pseudoobstruction		17%		2%
	Opsoclonus-myoclonus syndrome				
	Lambert Eaton myasthenic syndrome			100%	
	Brainstem encephalitis		19%		
	Acquired peripheral nerve hyperexcitability syndrome		Peripheral nerve hyperexcitability 17% (Morvan's syndrome 3%)		5%
	Stiff person syndrome	✓	3%		
	Myasthenia gravis				100%
Encephalomyelitis = multitude of levels of nervous system involved			✓		
Neurological manifestation	Seizures	76%	58%		
	Cognitive dysfunction & psychiatric symptoms	Psychiatric (including anxiety, agitation, bizarre behaviour, delusions, paranoia, hallucinations), or memory loss 100%	Cognitive impairment 71%, hallucinations 10%, frontosubcortical features 13%, depression or agitation 13%		
	Movement disorder	Any type 86% Orofacial dyskinesia 55%, Choreoathetoid and complex movements 47%, abnormal posturing or increased tone 47%	Parkinsonism 11%, tremor 7%, chorea 4%		
	Myelopathy		1%		
	Peripheral neuropathy		Sensory or motor14%		
	Autonomic dysfunction	Autonomic instability 69%	33%	Dry mouth 85%, male impotence 77%, dry eyes 30%, constipation 28%	2%
% of antibody positive patients with other clinical features		Decreased consciousness progressing to catatonic like state in 88%. Central hypoventilation 66%	Common hypothalamic symptoms, including hyponatraemia 36%, dyssomnia 26%, and hyperphagia 7%.		Eight patients had concurrent inflammatory myopathy with generalised myasthenia gravis
Reference		Dalmau (2008)[20], 100 patients (9M, 91F). CSF antibody positivity 93%	Tan (2008)[21], 72 patients (35M, 37F) with titre >0.1nmol/L	Titulaer (2008)[12], 51 patients (34M, 17F)	Vernino (2004)[22], 124, (45M, 79F)

Classical paraneoplastic syndromes are shaded in blue. ✓ = case series documents manifestation but does not publish number of cases.

Appendix III