Review article

PARANEOPLASTIC SYNDROMES

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ABSTRACTS

The term Paraneoplastic Syndromes (PNS) refers to symptoms or signs resulting from damage to organs or tissues that are remote from the site of a malignant neoplasm or its metastases. Widely known examples include cancer cachexia, hypercalcemia,Cushing's syndrome,and Trousseau's syndrome . A particularly devastating form of paraneoplastic syndromes ia a group of disorders classified as Paraneoplastic Neurological Disorders (PND).The incidence of PNS varies with the neurological syndrome and with the tumor. PNS can occurs in 7 to 10% of all patients with cancer. A paraneoplastic syndrome may result from production and release of antibodies and physiologically active substances, or it may be idiopathic. However, not all paraneoplastic syndromes are associated with these antibodies. Symptoms can be atypical, psychiatric, or even fluctuating, and PNS should often be in the differential diagnosis of otherwise unexplained neurological syndromes. An international panel of neurologists has established diagnostic criteria that divide patients with a suspected PNS into definite and probable categories. These criteria are based on the presence or absence of cancer, the presence of well-characterized antibodies, and the type of clinical syndrome. Detection of a "well-characterized" paraneoplastic antibody is extremely helpful because it proves the paraneoplastic etiology of the neurological syndrome. Usually, the paraneoplastic syndromes are divided into the following categories: (1) miscellaneous (nonspecific), (2) rheumatologic, (3) renal, (4) gastrointestinal, (5) hematologic, (6) cutaneous, (7) endocrine, and (8) neuromuscular. Treatment varies with the type and location of the paraneoplastic disorder, consist of treatment of the underlying tumor, as well as the treatment of the presumptive immune-mediated disorder is based on immunosuppression. Because paraneoplastic syndromes differ widely from individual to individual, prognosis may vary greatly.

Keywords: paraneoplastic syndrome, paraneoplastic neurological disorders, well-characterized antibodies

INTRODUCTION

The term PNS refers to symptoms or signs resulting from damage to organs or tissues that are remote from the site of a malignant neoplasm or its metastases. Paraneoplastic syndromes can affect most organs and tissues. Widely known examples include cancer cachexia, hypercalcemia,Cushing's syndrome,and Trousseau's syndrome.[1] The term paraneoplastic comes from the Greek roots para (alongside or near), neo (new), and plastic (being formed or shaped), and thus means "beside a new formation, or cancer." These syndromes can affect any organ or tissue, including the liver, skin, and muscles, but the nervous system itself is a common site.[2] 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.[3] Among the best characterized of the PNS are those producing polypeptide hormones such as Adrenocorticotropin (ACTH) or parathyroid hormone that affect organ function at remote sites. A particularly devastating form of paraneoplastic syndromes ia a group of disorders classified as PND which affect the brain and central nervous system and they are degenerative process in nature.[4]

These syndromes may occur in up to 10 – 15% (2 – 20% according to several reports) of malignancies, and they may be the first or most prominent manifestation. However, this incidence could be underestimated. The real incidence of deaths and complications related to paraneoplastic syndromes is unknown. No race predilection is reported. No sex predilection is known. People of all ages may be affected by cancers and their related paraneoplastic syndromes.[3] It is estimated that 7 – 10% of all patients with cancer will present with signs and symptoms of a paraneoplastic condition at the time of tumor diagnosis, although as many as 50% of these individuals may experience such a disorder at some point during their illness. The symptomatic manifestations of paraneoplastic syndromes may pose the most troublesome and threatening clinical problems that patients with cancer face. Diagnosis and treatment of paraneoplastic conditions can, therefore, contribute to an improved qualify of life, and in some cases,prolong life.[5]

The importance of the paraneoplastic syndromes (including hormones detected by immunoassay) and the elucidation of their mechanisms are important for many reasons. Their appearance may be the first sign of a malignancy, which allows its early detection in a curable state. They may simulate metastatic disease and prevent patients from having curative therapy. Conversely, treatable complications of malignancy *(e.g.,* metastatic disease, infection) may be ascribed to a paraneoplastic syndrome, leading to the withholding of appropriate therapy. They can be used as tumor markers in previously treated patients to detect early recurrence or in patients undergoing adjuvant therapy to guide further therapy. In patients with metastatic disease, their syndromes can be disabling, and appropriate treatment of the paraneoplasia may be the best means of palliating patients. The hormones released by tumors may be required for tumor growth (i.e., the tumor may produce its own growth factors and "autostimulate"), and appropriate identification of such hormones may allow a new rational therapeutic approach to the treatment of the neoplasms.[4,6]

INCIDENCE

The incidence of PNS varies with the neurological syndrome and with the tumor. PNS can occurs in 7 to 10% of all patients with cancer.[7] Approximately 10% of patients with plasma cell disorders accompanied by malignant monoclonal gammopathies are affected by a paraneoplastic peripheral neuropathy. More than half of the patients with the rare osteosclerotic form of myeloma develop a severe predominantly motor paraneoplastic peripheral neuropathy. In other hematological malignancies, the incidence of PNS is very low, with the exception of Hodgkin's disease. However, the incidence of PNS even in Hodgkin's disease is well below 1%. In solid tumors, the more common neurological syndromes are myasthenia gravis, which occurs in 15% of patients with a thymoma, and LEMS, which affects 3% of patients with SCLC. For other solid tumors, the incidence of PNS is < 1%.[8]

Nearly 90% of patients have associated cancer that is small cell lung cancer in nearly all cases. In our series, 10 of 11 patients had small cell lung cancer. Although the anti-Hu syndrome has a rare prevalence (probably < 1 % of patients with small cell lung cancer, the knowledge of the existence of this entity and how it presents should be relevant to radiologists because such knowledge will direct the investigation toward the search for a specific cancer-namely, lung cancer. Approximately 16% of patients with small cell lung cancer and no neurologic dysfunction have a detectable level of anti-Hu antibody in their sera. However,

this level is significantly lower than in patients who have small cell lung cancer and paraneoplastic neurologic dysfunction. In some patients with anti-Hu "paraneoplastic" syndrome, no tumor is detected, as was the case for nine (13%) of 71 patients in the study by Dalmau, et al.[9] and for one patient of our series.

The frequency of neurological paraneoplastic syndromes is something less than 0.5 per 100 000 population per year. Over the last 10 years, there has been increasing understanding of their immunological mechanisms and many new antigens/antibodies have been described. It is likely that the next few years will see the description of even more and so the number of 'antibody negative' cases will continue to shrink.[10]

PATHOPHYSIOLOGY

The relationships between malignancies and other diseases are complex and intriguing. As already reported, a paraneoplastic syndrome may result from production and release of antibodies and physiologically active substances, or it may be idiopathic. In fact, any tumor may produce hormones and protein hormone precursors, or a variety of enzymes and fetal proteins, or cytokines. More rarely, the tumor may interfere with normal metabolic pathways or steroid metabolism. Several cancers also produce fetal proteins that are physiologically expressed in embryonic cells during fetal life but not expressed by normal adult cells. These substances may help laboratories detect malignancies and usually are used as tumor markers (e.g., Carcinoembryonic Antigen [CEA], alpha-fetoprotein [AFP], cancer antigens [CA 19.9]).[3]

Currently, the mechanisms of how cancers affect distant sites are not understood precisely. 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 stimulate the onset of paraneoplastic disorders. However, not all paraneoplastic syndromes are associated with these antibodies. In the future, physicians who deal with cancer-associated syndromes should be able to differentiate the paraneoplastic syndromes and the benign disorders that mimic paraneoplastic syndromes. Recent advanced thought that most or all paraneoplastic neurologic disorders are immune-mediated. The mechanism entails ectopic expression by a tumor of an antigen that normally is expressed exclusively in the nervous system. Some of these so called onconeural antigens are also expressed in the normal testis, an organ that is, like the brain, an immunologically privileged site. The tumor antigen is identical to the neural antigen, but for unknown reasons the immune system identifies it as foreign and mounts an immune attack. The immune attack controls the growth of the cancer and may in a few instances obliterate it. However, the antibodies and cytotoxic T cells that are specific for the tumor antigen are not sufficient to cause the neurologic disease unless they cross the blood brain barrier and react with neurons expressing the onconeural antigen.[1] This process then sets up an inflammatory response in the neural tissue. In most cases the actual immunopathogenic mechanism is uncertain because passive transfer of the antibodies to animals does not reproduce the clinical syndrome, or the pathology.[10]

The discovery of paraneoplastic antineuronal autoantibodies resulted in the general belief that these are immune-mediated disorders triggered by aberrant expression of onconeural antigens in the tumor. Support for this hypothesis comes from the fact that the target paraneoplastic antigens are expressed both in the tumor and in the affected parts of the nervous system. Furthermore, the tumors are usually small and heavily infiltrated with inflammatory cells, and spontaneous remissions at the time of neurological presentation have been described. These findings suggest that some PNS without an identifiable tumor may result from immune-mediated eradication of the tumor. In keeping with this hypothesis, one study found more limited disease distribution and better oncologic outcome in Small Cell Lung Cancer (SCLC) patients with paraneoplastic

autoantibodies .Although the paraneoplastic antibodies are synthesized intrathecally, a pathogenic role could only be proved for those paraneoplastic autoantibodies that are directed against easily accessible antigens located at the cell surface. Examples of such antigens are the acetylcholine receptor (anti-AChR muscle type in myasthenia gravis and neuronal ganglionic type in autonomic neuropathy), P/Q-type voltage-gated calcium channels (anti-VGCC in Lambert-Eaton Myasthenic Syndrome [LEMS]), voltagegated potassium channels (anti-VGKC in neuromyotonia), and the metabotropic glutamate receptor mGluR1 (anti-mGluR1 in paraneoplastic cerebellar degeneration [PCD]). Most paraneoplastic antigens are located in the cytoplasm (e.g., the Yo antigen) or nucleus (e.g., the Hu and Ri antigens), and a pathogenic role for the respective antibodies has not be demonstrated In these disorders, indirect lines of evidence support the view that the cellular immune response against these antigens is responsible for the neurological damage. The relative contribution of the cellular and humoral immunity to the clinical and pathological manifestations has not been resolved The paraneoplastic antibodies may, in these cases, be surrogate markers for T-lymphocyte activation.[8]

The mechanism by which T cells recognize antigens expressed in neurons (which in normal circumstances lack expression of the antigen presenting molecules of major histocompatibility complex classes I and II) is unknown. It is possible that these inflammatory infiltrates are not the primary causes of the neuronal damage but a consequence of the antineural antibody that causes neural dysfunction. Because neuronal dysfunction can result in expression of major histocompatibility complex molecules, the T-cell infiltrates would be "second hit" resulting in neuronal loss. To date, however, an animal model is lacking. Immunization of animals with purified recombinant HuD fusion protein has not reproduced the disease.[10,11] Antibodies appear to be necessary but not sufficient alone to cause neurologic dysfunction, and cytotoxic T-cell responses are also involved. In this patient, identification of any of the a known antibodies would confirm the diagnosis of a paraneoplastic syndrome; depending on the antibody identified, this finding would also direct the search for the tumor. In approximately 40% of patients, no antibodies are identified.[12]

A totally different mechanism seems at work in PCD in Hodgkin's lymphoma because the target antigens of the associated anti-Tr and anti mGluR1 autoantibodies are not expressed in Hodgkin's tumor tissue. Dysregulation of the immune system in Hodgkin's lymphoma and an etiologic role for (viral?) infections have been postulated in this disorder.[8]

A constellation of symptoms is defined as a paraneoplastic syndrome when it is associated with the presence of actively growing tumor that elaborates a factor in excess into circulation, which, upon removal by tumor resection, results in the alleviation of systemic symptoms. By definition, such a factor should be overexpressed in tumor cells in vivo and or produced by tumor cells in vitro. Many of these factors are proteins that are normally secreted to act locally in a paracrine fashion. However, when markedly overproduced by tumor cells, they enter the circulation and act on tissue distant from the production site.[5]

Hematologic abnormalities as PNS include erythrocytosis, anemia, neutrophilia, neutropenia, eosinophilia, thrombocytosis, thrombocytopenia, venous thromboembolism and Disseminated Intravascular Coagulation (DIC). These abnormalities are, by and large, due to the production of biologically active growth factors, hormones or as yet unidentified "humors" by the tumor. As our understanding of growth factors controlling hematopoiesis has increased in recent years, the biologic basis of hematologic PNS are better understood. For instance, tumor-associated neutrophilia is now known to be caused by the production of G-CSF by the tumor. The mechanism by which tumor causes thromboembolism have also been extensively investigated. Cancer cells induce

platelet aggregation both in vitro and in vivo. Platelet aggregating material has been isolated and partially characterized from tumor cells. The involvement of platelet glycoprotein II b/IIIa in the tumor-platelet interaction has also been shown. Malignant cells contain a unique procoagulant, cancer procoagulant A, that directly activates factor X. Together with tissue factor, this procoagulant appears to have been contribute to a high incidence of thromboembolism in cancer patients. Better understanding of hematologic PNS is important for clinical care of the patients with cancer.[13,14]

Increased comprehension of the molecular mechanisms of paraneoplastic syndromes will permit earlier diagnoses of cancer and also be useful for following the response to antineoplastic therapy, using cancer products as tumor markers of the progression or remission of disease. As on figure below proposed pathogenesis of paraneoplastic neurologic disorders is depicted. A tumor not involving the nervous system expresses a neuronal protein that immune system recognized as nonself. In the illustration, antibodies are reacting with volate-gated calcium channelsat the neuromuscular junction, causing the Lambert-Eatern myasthenic syndrome.[6]

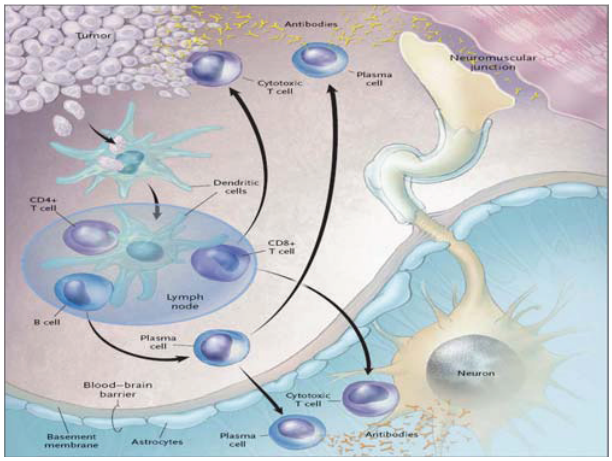

Figure 1. Proposed pathogenesis of PNS[6]

DIAGNOSIS AND UNDERLYING CAUSES

The causes of the paraneoplastic syndromes associated with underlying cancers are not well known. Only a few cases clearly demonstrate an etiologic and a pathogenetic factor. Current evidence suggests that most paraneoplastic syndromes are the result of the way in which our immune systems respond to cancer. According to this hypothesis, the process starts with proteins normally present only in nerve cells. These proteins are also found, for unknown reasons, in some cancers. In nerve cells the proteins are probably essential for growth and maintenance, so they may also be essential for those cancers' growth. When a person's immune system senses a tumor growing in the body, it can respond by identifying those cancerous cells and the crucial protein or proteins within them as foreign, or "nonself." The immune system thus responds with an attack on each protein and all the cells that contain it. The immune attack, if it is vigorous enough, can slow the growth of the tumor, but it also attacks the nerve cells that normally contain the protein(s). As a result, a person can develop severe nervous system problems, such as memory loss, lack of coordination, and weakness. Meanwhile, the growth of the cancer may be slowed so successfully that it becomes small and difficult to detect by conventional means.[2]

Clinical syndromes are never pathognomonic for a paraneoplastic etiology, and a high index of clinical suspicion is important. Symptoms can be atypical, psychiatric, or even fluctuating, and PNS should often be in the differential diagnosis of otherwise unexplained neurological syndromes.[8]

Even if its causes are not known, fever is considered to result from the release of endogenous pyrogens (ie, lymphokines or tissue pyrogenes). Fever also may be related to necrotic-inflammatory phenomena of the tumor and/or to alterations in liver function and consequent disorders of steroidogenesis. Dysgeusia seems to be related to alterations in the

body's level of copper and zinc or to a morphofunctional variation of the tasting bodies (ie, gustative papillae). Cachexia is thought to be caused by bioactive molecules produced by the tumor, such as alpha-lymphotoxin (Tumor Necrosis Factor [TNF] alpha), peptides, and nucleotides, which are able to affect metabolism. Such modifications include increase in the serum levels of fatty acids; decrease of urea, alanine, and carbon dioxide; and alterations of glucose metabolism. Cytokines, growth factors, immunecomplexs and other active substances may or may not play a parts in other paraneoplastic syndromes such as renal, hematological and gastrointestinal.[3,4]

The blood of many, but not all, people suffering from neurological paraneoplastic syndromes contains antibodies that the immune system has produced in response to specific proteins. The presence of such antibodies can tell physicians that a person's neurological disorder is paraneoplastic; it can also indicate the probable site of the cancer that is at the root of the trouble.[2]

Although paraneoplastic syndromes affecting the nervous system can cause a bewildering variety of symptoms, they tend to share certain characteristics that help doctors identify them:

1. The neurological signs and symptoms usually appear rapidly-within a matter of days, weeks, or a few months. In contrast, degenerative diseases like Parkinson and Alzheimer develop gradually, over years.
2. The neurological signs usually precede those of the cancer, which is often extremely small and difficult to detect.
3. The neurological disorder usually causes severe disability. Many people with cerebellar degeneration become unable to walk. Many people with limbic encephalitis cannot function because they cannot remember ongoing events. While the cancer may still be restricted to one corner of the body, the immune response to that cancer is thorough and systematic.

Diagnosing a neurological syndrome as paraneoplastic requires the exclusion of other possible causes by a reasonably complete workup. Because of the difficulties in diagnosis, an international panel of neurologists has established diagnostic criteria that divide patients with a suspected PNS into definite and probable categories. These criteria are based on the presence or absence of cancer, the presence of well-characterized antibodies, and the type of clinical syndrome.[8,15]

Patients with a definite PNS include those with:[8]

(a) A classical syndrome (i.e., encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, LEMS, or dermatomyositis) and cancer that develops within 5 years of the diagnosisof the neurological disorder, regardless of the presence of
paraneoplastic antibodies.

(b) A nonclassical syndrome that objectively improves or resolves after cancer treatment, provided that the syndrome is not susceptible to spontaneous remission

(c) A nonclassical syndrome with paraneoplastic antibodies (well characterized or not) and cancer that develops within 5 years of the diagnosis of the neurologi-cal disorder.

(d) A neurological syndrome (classical or not) with well-characterized paraneoplastic antibodies (i.e., anti-Hu, anti-Yo, anti-Ri, antiamphiphysin, anti-CV2, or anti-Ma2).

Patients with a possible PNS include those with :

(a) A classical syndrome without paraneoplastic anti-bodies and no cancer but at high risk to have an underlying tumor (e.g., smoking habit).

(b) A neurological syndrome (classical or not) without cancer but with partially haracterized paraneoplastic antibodies.

(c) A nonclassical neurological syndrome, no paraneo-plastic antibodies, and cancer that presents within 2 years of the neurological syndrome.

Differential diagnosis[4]

The importance and frequency of paraneoplastic syndromes make it imperative to establish the appropriate diagnosis. If the cause of the paraneoplastic syndrome is unknown, this may mean excluding all other known causes of the syndrome. In general, paraneoplastic syndromes must be differentiated from:

1. Direct invasion by the primary tumor or its metastases
2. Obstruction caused by tumor or tumor products
3. Vascular abnormalities
4. Infections
5. Fluid and electrolyte abnormalities
6. Toxicity of cancer therapy, including cytotoxic chemotherapy, radiation therapy, immunotherapy, or antibiotic therapy.

Laboratorium findings

Once a paraneoplastic diagnosis has been established or is suspected, rapid dentification of the tumor becomes essential but may be difficult because most PNS develop in the early stages of cancer. The workup generally starts with a detailed history, including smoking habits, weight loss, night sweats, and fever. A thorough physical examination should include palpation for pathological lymph nodes, rectal and pelvic examination, and palpation of breasts and testis. Often, the tumor is detected by high-resolution Computed Tomography (CT) of the chest, abdomen, and pelvis. If the CT scan remains negative, whole-body Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) or PET/CT is recommended to detect an occult tumor or its metastases . In addition, the type of antibody and PNS may suggest a specific underlying tumor and indicate further diagnostic tests, such as mammography (maybe replaced by MRI) or ultrasound of the testes or pelvis . When all tests remain negative, repeat evaluation at 3 to 6 month intervals for 2 – 3 years is recommended.[8]

Patients with a suspected paraneoplastic disorder should receive a complete panel of laboratory studies of blood, urine, and CSF. CBC counts may demonstrate anemia. This anemia may be the result of any of several different types of cancer, or it may be the result of different benign conditions. A platelet count must be performed in any patient with symptoms of DIC.

Blood enzymes may be altered, even in healthy individuals or those who have benign conditions. Tumor markers are very useful for diagnosis of cancers that are clinically silent, but most markers are not specific for determining the origin of the cancer.[3]

Many patients with paraneoplastic disorders may have autoantibodies against several tissues of the body. Demonstration of these autoantibodies is very important to confirm the diagnosis of a paraneoplastic syndrome and distinguish it from non neoplastic forms. Most known autoantibodies are directed against nervous system structures. Detection of a "well-characterized" paraneoplastic antibody is extremely helpful because it proves the paraneoplastic etiology of the neurological syndrome. The paraneoplastic antibodies are generally divided into three categories. The well-characterized antibodies are reactive with molecularly defined onconeural antigens. These antibodies are strongly associated with cancer and have been detected unambiguously by several laboratories in a reasonable number of patients with well-defined neurological syndromes. The partially characterized antibodies are those with an unidentified target antigen and those that have either been described by a single group of investigators or have been reported in only a few patients. The third group consists of antibodies that are associated with specific disorders but do not differentiate between paraneoplastic and nonparaneoplastic cases.[8]

Imaging studies

Any possible imaging study may be useful to detect the primary tumor in patients with paraneoplastic disorders. CT scanning and magnetic resonance imaging of the whole body allow detection of the site and the extension of the underlying primary tumor and

Tabel 1. Antibodies, clinical syndromes, associated tumors[8]

Antibody	Clinical syndromes	Associated tumors
Well-characterized paraneoplastic antibodies		
Anti-Hu (ANNA-1)	Encephalomyelitis, limbic encephalitis, sensory neuronopathy, subacute cerebellar degeneration, autonomic neuropathy	SCLC, neuroblastoma, prostate
Anti-Yo (PCA-1)	Subacute cerebellar degeneration	Ovary, breast
Anti-CV2 (CRMP5)	Encephalomyelitis, chorea, limbic encephalitis, sensory neuronopathy, sensorimotor neuropathy, optic neuritis, subacute cerebellar degeneration, autonomic neuropathy	SCLC Thymoma
Anti-Ri (ANNA-2)	Opsoclonus-myoclonus, brainstem encephalitis	Breast, SCLC
Anti-Ma2 (Ta)[a]	Limbic/diencephalic/brainstem encephalitis, subacute cerebellar degeneration	Testicle, lung
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis, subacute sensory neuronopathy, sensorimotor neuropathy	Breast, SCLC
Anti-recoverin	Cancer-associated retinopathy	SCLC
Partially characterized antibodies		
Anti-Tr (PCA-Tr)	Subacute cerebellar degeneration	Hodgkin's disease
ANNA-3	Encephalomyelitis, subacute sensory neuronopathy	SCLC
PCA-2	Encephalomyelitis, subacute cerebellar degeneration	SCLC
Anti-Zic4	Subacute cerebellar degeneration	SCLC
Anti-mGluR1	Subacute cerebellar degeneration	Hodgkin's disease
Antibodies that occur with and without cancer		
Anti-VGCC	Lambert-Eaton myasthenic syndrome, subacute cerebellar degeneration	SCLC
Anti-AchR	Myasthenia gravis	Thymoma
Anti-nAChR	Subacute autonomic neuropathy	SCLC
Anti-VGKC	Limbic encephalitis, neuromyotonia	Thymoma, SCLC

[a]Brainstem encephalitis and subacute cerebellar degeneration are usually associated with tumors other than testicular cancer and sera from these patients also react with the Ma1 protein.
Abbreviations: AChR, acetylcholine receptor; ANNA, antineuronal nuclear antibody; mGluR1, metabotropic glutamate receptor type 1; nAChR, nicotinic acetylcholine receptor; PCA, Purkinje cytoplasmic antibody; SCLC, small cell lung carcinoma; VGCC, voltage-gated calcium channels; VGKC, voltage-gated potassium channel.

its metastases, if present. Scintigraphy may be useful in patients with endocrine disorders related to a hormone-producing tumor. Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) scanning may be performed to evaluate patients with neurologic disorders. These examinations allow differentiation of paraneoplastic and nonparaneoplastic neurologic disorder.[3,8,16,17] Endoscopy is useful to detect tumors of the respiratory tree and of the digestive tract, and it also allows the examiner to obtain biopsy samples.[3]

Pathological features

Another factor complicating our understanding of the neuronal degeneration in paraneoplastic neurologic disorders is the fact that the pathological features of these disorders vary widely. For example, in paraneoplastic cerebellar degeneration, there is total loss of the Purkinje cells of the cerebellum, with little or no pathological change elsewhere in the nervous system and no identifiable inflammatory infiltrates within the cerebellum itself. By contrast, in paraneoplastic

encephalomyelitis, there is not onlywidespread destruction of neurons, including Purkinje cells, but also florid inflammation within the central nervous system and intraneuronal deposits of antibodies. In some patients with paraneoplastic syndromes, particularly opsoclonus–myoclonus, autopsy may demonstrate an entirely normal brain.[1,16]

CLINICAL SYNDROMES

Because of their complexity and variety, the clinical pictures of these syndromes may vary greatly. Paraneoplastic syndromes may or may not be characteristic of a specific system. Usually, the paraneoplastic syndromes are divided into the following categories: (1) miscellaneous (nonspecific), (2) rheumatologic, (3) renal, (4) gastrointestinal, (5) hematologic, (6) cutaneous, (7) endocrine, and (8) neuromuscular.

A complete history and physical examination can suggest neoplasia. Persons with a family history of malignancies (eg, breast, colon) may be at increased risk and should be screened for cancer. Nonspecific syndromes can precede the clinical manifestations of the tumor, and this occurrence is a negative prognostic factor.[3]

Miscellaneous (nonspecific)[3]

- Fever, dysgeusia, anorexia, and cachexia are included in this category.
- Fever frequently is associated with lymphomas, acute leukemias, sarcomas, renal cell carcinomas (Grawitz tumors), and digestive malignancies (including the liver).
- Generally, fever occurs in the evening and is of a continual-remittent type.
- Dysgeusia manifests in a variety of ways, from ageusia to aversion to protein (in particular, meat proteins).
- Anorexia is a common disorder among patients with neoplastic syndromes and is responsible, along with dysgeusia, for weight loss and even cachexia.

Rheumatologic[18]

- Paraneoplastic arthropathies arise as rheumatic polyarthritis or polymyalgia, particularly in patients with myelomas; lymphomas; acute leukemia; malignant histiocytosis; and tumors of the colon, pancreas, prostate, and CNS.
- With lung cancers, pleural mesothelioma, phrenic neurilemmoma, and hypertrophic osteoarthropathy may be observed in as many as 95% of cases.
- In some cases, the tumor can be preceded by scleroderma, with its peculiar clinical manifestations.
- The widespread form is typical of malignancies of the breast, uterus, and lung (both alveolar and bronchial forms).
- On the other hand, the localized form is characteristic of carcinoids and of lung tumors (bronchoalveolar forms).
- Patients with lymphomas or cancers of the lung, breast, or gonads may have systemic lupus erythematosus (SLE).
- Patients with myeloma, renal carcinoma, and lymphomas may present, although rarely, with secondary amyloidosis of the connective tissues Hypertrophic osteoarthropathy presents with digital clubbing and painful swelling of the hip, wrist, and knee, accompanied by an articular effusion.
- Sometimes, the long bones also are involved. In such cases, patients complain of pain and present a typical elevation (thickening and detachment) of the periosteum on X-ray.
- For patients with scleroderma or systemic lupus erythematosus (SLE), the clinical picture is characteristic of nonparaneoplastic conditions.

Renal[19,20]

- Patients with tumors that secrete Adrenocorticotropic Hormone (ACTH) or ACTH-like substances may have hypokalemic nephropathy, which is characterized by urinary potassium leakage of more than 20 mEq per 24 hours. This occurs in 50% of individuals with ACTH-secreting tumors of the lung (ie, small cell lung cancer).

- Other types of tumors that can produce ACTH, antidiuretic hormone (ADH), and gut hormones may cause hypokalemia, hyponatremia or hypernatremia, hyperphosphoremia, and alkalosis or acidosis
- Nephrotic syndrome is observed, although seldom, in patients who have Hodgkin lymphoma (HL); non-Hodgkin lymphoma (NHL); leukemias; melanomas; or malignancies of lung, thyroid, colon, breast, ovary, or pancreatic head.
- Patients with myeloma, renal carcinoma, or lymphomas present rarely with secondary amyloidosis of the kidneys, heart, or CNS. The clinical picture of secondary amyloidosis is related to renal and cardiac injuries.
- Co-existence of subacute thyroiditis and renal cell carcinoma as a PNS.

Gastrointestinal[20]

- Watery diarrhea accompanied by an electrolyte imbalance leads to asthenia, confusion, and exhaustion.
- These problems are typical of patients with proctosigmoid tumors (both benign and malignant) and of medullary thyroid carcinomas (MTCs) that produce several prostaglandins (PGs; especially PG E2 and F2) that lead to malabsorption and, consequently, unavailability of nutrients.
- These alterations also can be observed in patients with melanomas, myelomas, ovarian tumors, pineal body tumors, and lung metastases.

Hematologic[21]

- Symptoms related to erythrocytosis or anemia, thrombocytosis, disseminated intravascular coagulation (DIC), and leukemoid reactions may result from many types of cancers. The most prominent clinical picture of paraneoplastic disorders affecting the hematopoietic system is similar to a clinical picture that is not related to tumors.
- Thrombocytosis (> 500,000 platelets per dl) can be observed in patients with cancer of the lung, breast, digestive organs, or reproductive organs. This thrombocytosis leads to the following 2 types of phenomena: (1) migrating thrombophlebitis that is resistant to standard anticoagulant therapy and involves the arm veins, the inferior vena cava, and the jugular veins and usually appears as oval formations along the little and middle veins, accompanied by cutaneous necrosis and (2) marantic (nonbacterial) endocarditis characterized by growths developing on the heart valves that may break and form clots and emboli.
- In some cases, symptoms result from migrating vascular thrombosis (ie, Trousseau syndrome) occurring in at least 2 sites.
- Leukemoid reactions, characterized by the presence of immature WBCs in the bloodstream, usually are accompanied by hypereosinophilia and itching. These reactions typically are observed in patients with lymphomas or cancers of the lung, breast, or stomach. Patients with lung cancer or pleural mesothelioma may have cryoglobulinemia.

Cutaneous[23]

- Itching is the most frequent cutaneous manifestation in patients with cancer.
- Herpes zoster, ichthyosis, flushes, alopecia, or hypertrichosis also may be observed. Herpes zoster and alopecia presenting as part of a paraneoplastic syndrome are similar to their equivalent benign forms.
- Acanthosis nigricans and dermic melanosis are characterized by a blackish pigmentation of the skin and usually occur in patients with metastatic melanomas or pancreatic tumors. Acanthosis nigricans and dermic melanosis often are pathognomonic for the presence of a malignancy. They are similar but differ by location. Dermic melanosis is diffuse; acanthosis nigricans usually is accompanied by confluent papillomas and affects the oral, umbilical, axillary, and inguinal areas. Three types of acanthosis nigricans are described benign, pseudoacanthosis, and malignant. The malignant form is characterized by rapid growth of hyperkeratotic warts (Leser-Trélat sign).

- Flushes appear that are similar to those related to benign conditions such as stress.
- Hypertrichosis is not different from the form it takes when related to an endocrine imbalance (usually related to adrenal dysfunction). Paraneoplastic hypertrichosis is characterized by a sudden appearance of wooly hair on the face and ears that suddenly disappears after the tumor is removed.
- Ichthyosis, which in the early stages could mimic a benign dermatosis, is characterized by desquamation of the extensory surface of the limbs (resembles the scales of a fish, in ancient Greek *ichtus* means fish)[22]
- Patients with glucagonoma may have necrotizing migrating erythema (NME) resulting from erythematous and exfoliative injuries that differ from exfoliative erythrodermia. This is typical of leukemias and lymphomas and results in blushing and diffuse skin desquamation that affects cutaneous adnexa, which subsequently results in alopecia and nail fragility but which rarely is accompanied by fever, chills, and itching.
- Patient with CLL presenting pemphigus paraneoplastic as the initial presentation.

Endocrine[24]

- Endocrine symptoms related to paraneoplastic syndromes usually resemble the more common endocrine disorders (eg, Cushing syndrome). Cushing syndrome, accompanied by hypokalemia, very high plasma ACTH levels, and increased serum and urine cortisol concentrations, is the most common example of an endocrine disorder linked to a malignancy. This is related to the ectopic production of ACTH or ACTH-like molecules from many tumors (eg, small cell cancer of the lung). Patients with Cushing syndrome as part of a paraneoplastic syndrome appear similar to patients with Cushing disease, with the typical moon facies and obesity of the trunk. Symptoms caused by human chorionic gonadotropin and urinary gonadotropin peptide are absent. Gynecomastia may occur in males.
- Hyponatremia and hypercalcemia may occur in patients with tumors that are producing hormones that affect water and electrolytic balance (ie, ADH and Parathyroid Hormone [PTH]-like molecules).
- Hypoglycemia seems related to production of Insulinlike Growth Factor (IGF)-1 and IGF-2.
- Production of beta HCG by spermatic cord leiomyosarcoma as a PNS.

Neuromuscular (paraneoplastic neurologic disorders)[25]

- One or more neurological paraneoplastic syndromes may be present in patients with cancer, especially those suffering from lung cancer. Each part of the nervous system can be affected, with sensory, motor, or mixed neuropathies.
- Sensory neuropathy, usually related to lung cancer only, originates from ganglionic degeneration, and its onset is characterized by paresthesias and tabetic-like pain, acute hyporeflexia with a reduction of proprioceptive sensitivity and ataxia (both static and dynamic), vibratory anesthesia, deafness, cutaneous hypoesthesia or anesthesia, dysgeusia, and dysosmia.
- Mixed neuropathy appears with several malignancies and has an extremely variable presentation, with motor or sensory symptoms either preceding the clinical onset of tumor disease or accompanying it. The spinal cord can be affected by either subacute necrotic myelitis or subacute myelitis. These conditions lead to a progressive flaccid paraplegia with areflexia, lack of sphincteric control, and anesthesia of the lower limbs. A Lateral Amyotrophic Syndrome (LAS) may occur, presenting with the typical muscular asthenia and atrophy, hyperreflexia with pyramidal fasciculations, and degeneration of the second motor neuron. This form of LAS differs from the non paraneoplastic form because it includes sensory involvement (i.e., proprioception and pallesthesia).
- The cerebellum may be the site of subacute neuronal degeneration in patients with small cell carcinoma or breast or gynecologic tumors. Such degeneration

presents clinically with cerebellar ataxia, dysarthria, and nystagmus. Dysphagia, palpebral ptosis, deafness, and a positive Babinski sign also may occur. The cerebellum of patients with lung cancer also may be affected by encephalitis. In such cases, the clinical picture is characterized by convulsions, delirium, and a lack of long-term memory. In other patients, the pathological process involves the medulla (i.e., encephalomyelitis).

- In some patients with leukemias, lymphomas, or epithelial cancers, a rare degenerative process involving the semioval center may be observed. This degenerative process is characterized by convulsions, cerebellar ataxia, progressive dementia, aphasia, hemiparesis, hemihypoesthesia, dysphagia, and nystagmus. The process develops rapidly, leading to death within 6 months of onset.
- ELMS may occur in patients with lymphomas; thymomas; or cancers of the pancreas, rectum, kidney, breast, prostate, or uterus. ELMS may resolve after surgical resection of the primary tumor but not after radiotherapy or chemotherapy. Patients with lymphomas or cancers of the lung, stomach, breast, or uterus may have clinical manifestations of polymyositis and dermatomyositis that are characterized by asthenia, pain, and progressive hypertrophy of proximal muscles affecting, then involving, the dermis and the skin. This leads to violet-colored rashes of the face and hands.

Despite their clinical variety, there are a number of generalizations around the paraneoplastic syndromes:[10]

1. They present acutely or subacutely with progression over days to weeks.
2. Most patients are not known to have cancer at presentation but, if they are, the cancer is usually rather limited in extent.
3. The clinical presentation and the identification of serum antibodies help predict the likely tumour site in the majority of cases.
4. Cancer may take weeks to 5 years to become evident in some patients with positive serum paraneoplastic antibodies.
5. Disability is severe in most cases.
6. Neurological symptoms and signs are occasionally partially responsive to immunulogical treatments, or treatment of the underlying tumour.
7. Early identification of cancer and subsequent treatment may improve survival.

Table 2. Paraneoplastic neurological syndromes[8]

Central nervous system
Encephalomyelitis
Limbic encephalitis
Brainstem encephalitis
Subacute cerebellar degeneration
Opsoclonus-myoclonus
Stiff-person syndrome
Paraneoplastic visual syndromes
Cancer-associated retinopathy
Melanoma-associated retinopathy
Paraneoplastic optic neuropathy
Motor neuron syndromes
Subacute motor neuronopathy
Other motor neuron syndromes
Peripheral nervous system
Subacute sensory neuronopathy
Acute sensorimotor neuropath
Chronic sensorimotor neuropathy
Association with M-proteins
Subacute autonomic neuropathy
Paraneoplastic peripheral nerve vasculitis
Neuromuscular junction and muscle
Lambert-Eaton myasthenic syndrome
Myasthenia gravis
Neuromyotonia
Dermatomyositis
Acute necrotizing myopathy
Cachectic myopathy

*Classical paraneoplastic neurological syndromes are in italics.

TREATMENT

Treatment varies with the type and location of the paraneoplastic disorder. Two treatment options exist. The first therapeutic option is treatment of the underlying tumor,based on the usual surgery, radiation, or chemotherapy (singly or in combination). The therapeutic protocols are those that generally are applied to neoplastic disorders without the presence of paraneoplastic syndrome.The second option is the treatment of the presumptive immune-mediated disorder is based on immunosuppression (by intravenous immunoglobulins, steroids, or other immunosuppressive drugs or by plasma exchange).This treatment should be reserved for patients with clearly identifiable antibodies in their serum.The surgical procedures that usually are applied to neoplastic disorders also are applied to those with paraneoplastic syndrome. On the other hand, some paraneoplastic disorders may disappear rapidly without surgery on the primary tumor (e.g., in patients with hypertrophic osteoarthropathy, resection of the tumor or the ipsilateral vagus nerve leads to rapid remission of symptoms).[1,3]

Unfortunately, most paraneoplastic syndromes do not respond to treatment of either the tumor or the immune system. A person with such a condition may remain substantially disabled even when the tumor that created the problem has been treated effectively. The paraneoplastic syndrome may have brought that cancer to light and allowed early treatment of it, but the neurological problem itself remains, and the person must usually learn to deal with it as a chronic condition.[2]

Despite the immunological etiology of most of the PNS, the results of mmunotherapy have been disappointing. Exceptions are the neurological syndromes associated with paraneoplastic antibodies that are directed against antigens that are located at the surface of the cell (i.e., antigens that are accessible to circulating antibodies). These include not only disorders of the peripheral nervous system (LEMS, myasthenia gravis, and neuromyotonia) but also anti-mGluR1-associated PCD and antiamphiphysin-associated stiff-person syndrome. Immunotherapy modalities that are recommended for these disorders include plasma exchange, immunoadsorption (extraction of patient IgG over a protein A column), steroids, and iv Ig.[1,8]

PROGNOSIS

Because paraneoplastic syndromes differ widely from individual to individual, prognosis may vary greatly. For example, DIC indicates a poor prognosis, while hypertrophic osteoarthropathy is one of the few paraneoplastic syndromes that may improve a patient's prognosis. Some disorders, such as the Lambert–Eaton myasthenic syndrome and myasthenia gravis, respond well to immunosuppression and subsequently to treatment of the underlying tumor.[3]

The peripheral neuropathy associated with osteosclerotic myeloma generally resolves when the tumor is treated with radiotherapy. A few disorders, such as opsoclonus-myoclonus in adults, may respond to treatment of the underlying tumor, immunosuppression, or both, or they may resolve spontaneously. In many instances, it is not clear whether the paraneoplastic syndrome resolves spontaneously or in response to treatment. Disorders involving the central nervous system, such as encephalomyelitis associated with cancer or paraneoplastic cerebellar degeneration, usually respond poorly to treatment, although they may stabilize when the underlying tumor is treated. Patients with paraneoplastic syndromes appear to have a better prognosis with respect to the tumor than do patients with the same type of tumor who do not have paraneoplastic syndromes. The reason for the different prognoses probably has to do with the underlying pathologic features.

The Lambert-Eaton myasthenic syndrome and myasthenia gravis are diseases of the neuromuscular junction, which can recover its function once the causal insult has resolved, because there is no loss of the parent neuron. Disorders such as paraneoplastic cerebellar

degeneration are usually associated with neuronal loss, and because they evolve subacutely and treatment is often delayed, the neurons die, making recovery impossible. Some central nervous system disorders, such as opsoclonus-myoclonus, may not involve cellular loss and, in fact, may have no identifiable pathologic features. Thus, patients with these disorders, like those with the Lambert-Eaton myasthenic syndrome, have the potential for recovery. An important question is whether immunosuppression for treatment of the paraneoplastic syndrome stimulates the growth of the tumor. No evidence of this has been reported. Most reports that describe an absence of response of the paraneoplastic syndrome to immunosuppression do not note an exacerbation of the tumor.[1,3,6]

SUMMARY

PNS are uncommon diseases with different pathogenesis and clinical manifestations. Although these disorders are rare, the investigation of paraneoplastic syndromes has been fruitful for the clinical neurologist, the clinical oncologist, and the neuroscientist. The oncologist who encounters a patient with an antibody-positive paraneoplastic syndrome not only knows the area of the body in which to look for the tumor but also can estimate that the growth of the tumor is likely to be more indolent than the same tumor in a patient without paraneoplastic syndrome. This knowledge may have an influence on the therapy that the oncologist prescribes. The better described pathogenesis is the autoimmune one, characteristic of neurological, for which the clinical and laboratorium findings have been well supported. Paraneoplastic syndromes are important because their identification permits an early diagnosis of tumors and rapid treatment, with largely improved`prognosis and life expectancy for the patient. More study are necessary for a better definition of their clinical aspects and pathogenesis and to delineate standard guidelines for a diagnostic-therapeutic approach to these diseases.

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