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Update on paraneoplastic neurologic disorders

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Abstract

Once considered rare, paraneoplastic neurologic disorders (PNDs) are an extensive group of neurologic disorders that occur either exclusively or at increased frequency in patients with cancer. PNDs have been increasingly recognized due in large part to the identification of antineuronal antibodies in the serum and cerebrospinal fluid of patients. Although almost any neoplasm can cause PND, the tumors most commonly involved are small-cell lung cancer, cancers of the breast and ovary, thymoma, neuroblastoma, plasma cell tumors, and ovarian teratoma. Establishing the diagnosis of PND is important because in more than two-thirds of patients the neurologic symptoms develop before the presence of the cancer is known. When PND is suspected and no tumor is found, it is recommended that cancer screening be repeated every 6 months. Early diagnosis and intervention offers the best chance of neurologic stabilization or improvement.

Patients with systemic cancer often develop neurologic problems either as a result of direct involvement of the nervous system by tumor or through indirect mechanisms such as coagulopathies, infections, and metabolic and nutritional disturbances. Often the history, temporal association with cancer therapies, and results of ancillary tests will reveal one of these mechanisms as the etiology. It is the authors' experience that when no obvious cause of a neurologic problem is found, or if the syndrome is perplexing, the diagnosis often entertained is a paraneoplastic neurologic disorder (PND).

Once considered rare, PNDs are an extensive group of neurologic disorders that occur either exclusively or at increased frequency in patients with cancer. PNDs have been increasingly recognized in large part due to the identification of antineuronal antibodies in the serum and cerebrospinal fluid (CSF) of patients.

Once PND is presumed, serum and/or CSF are sent for testing for paraneoplastic antibody panels.¹ When negative, there is reinforcement of the idea that PNDs are rare. However, if cases are carefully selected using clinical criteria, the rate of positivity for antineuronal antibodies substantially increases. For example, of 60,000 consecutive cases with suspected PND, 553 (0.9%) were positive for antibodies associated with PND.² In contrast, of 649 cases consecutively studied in a research lab where most samples are preselected by use of clinical criteria, 163 (25%) were positive (Dalmau and Rosenfeld, unpublished observation).

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Diagnosis

Establishing the diagnosis of PND is important because in more than two-thirds of patients the neurologic symptoms develop before the presence of the cancer is known. For many patients, the signs and symptoms of PND are more debilitating than the cancer, and prompt recognition and treatment may reduce morbidity.

Most PNDs have characteristic clinical features that in the appropriate context should immediately raise suspicion for a paraneoplastic etiology.¹ For example, the likelihood that Lambert-Eaton myasthenic syndrome (LEMS) or subacute cerebellar degeneration in a middle-aged or elderly patient is paraneoplastic is probably more than 50%, whereas subacute sensory neuropathy and dermatomyositis are probably paraneoplastic in origin in less than 20% of patients, and myasthenia gravis in only about 10% of cases.^{3,4}

Table 1 lists the classic neurologic syndromes that suggest paraneoplasia. An adult patient who has the acute or subacute onset of one of these classic syndromes should be evaluated for an occult tumor regardless of antibody status; for a patient with a known cancer or who has recently gone into tumor remission, evaluation for recurrence is warranted.⁵ Although almost any neoplasm can cause PND, the tumors most commonly involved are small-cell lung cancer (SCLC), cancers of the breast and ovary, thymoma, neuroblastoma, plasma cell tumors, and ovarian teratoma.

The diagnosis of PND is more difficult in patients who develop less characteristic symptoms, especially if no antibodies are found in the serum or CSF. Table 1 lists neurologic syndromes that may be seen as PND but for which the relationship is not as strong as with the classic syndromes noted above. For patients with these syndromes, two features that support PND are an acute or subacute onset and the presence of inflammation in the CSF, including pleocytosis, elevated protein concentration, intrathecal synthesis of immunoglobulin, and oligoclonal bands.

For patients with cancer, neuroimaging of the involved part of the nervous system, in particular magnetic resonance imaging (MRI), helps to exclude metastasis and is abnormal in about 70% of patients with paraneoplastic limbic encephalitis. For patients without cancer, a search for a neoplasm is always warranted if PND is in the differential diagnosis.

Due to the common association of breast and gynecologic cancers with PND, mammogram and pelvic CT scan or ultrasound should be carried out in all women with a suspected PND. Whole body positron emission tomography (PET) scans may detect tumors that escape detection by other standard imaging methods.^{5,6} Men with symptoms of limbic and brainstem encephalitis should be examined for a testicular tumor, and young women for an ovarian teratoma, which may appear as a benign cyst. In both instances, ultrasound and CT of the abdomen and pelvis are useful to identify tumors of the gonads and retroperitoneal space.

For patients with classic PND, or those with less classic PND who are positive for paraneoplastic antibodies, in whom no tumor is found, it is recommended that cancer screening be repeated every 6 months. In general, a cancer will be identified within the first 4 years of the PND, but there are rare instances in which the expected type of tumor was found many years later.⁷

In some patients, such as those with anti-Ma2, anti-Yo, or anti-NMDA receptor antibodies in whom no tumor is found, surgical exploration or removal of the likely affected organ can be considered, especially if the patient is deteriorating despite aggressive immunomodulatory therapies. This is a complicated decision that may require input from

hospital ethicists, as these patients are often unable to provide consent. Surgery should be considered only after consultation at a tertiary care center with experience with these disorders.

The development of peripheral nerve dysfunction in cancer patients often raises the question of paraneoplasia. Nutritional deficits and hepatic or renal failure should be considered, especially in patients with advanced disease or significant weight loss. Leptomeningeal metastases often present with multifocal, asymmetric findings, including cranial nerve abnormalities and radiculopathy, while metastatic infiltration of nerves will often produce mononeuropathies or plexopathies rather than distal and symmetric sensory loss. A history of treatment with neurotoxic chemotherapies, MRI, CSF analyses, electrophysiologic features, and, less frequently, pathologic findings of nerve biopsy often clarify the etiology. Most cases of paraneoplastic neuropathy do not have associated antibodies.⁸

Immune responses in PND

Although the exact pathogenesis of PND is unclear, it is generally believed that expression of neuronal proteins by a cancer triggers immune responses that are misdirected against the nervous system and result in the neurologic deficits. In general, the immune responses are antineuronal antibodies that can be found in serum and CSF. The antibodies serve as markers of the paraneoplastic origin of the neurologic symptoms and, in some cases, of the presence of specific types of tumors (Table 2).

In some disorders, the antibodies are directly pathogenic (eg, anti-voltage-gated calcium channel [anti-VGCC] antibodies in LEMS), and their detection directs therapeutic approaches aimed at reducing antibody titers. However, PND may occur without associated antibodies, and paraneoplastic antibodies are occasionally found at low titers in a variable proportion of patients with cancer without PND^{9,10}; therefore, their presence should not be the only condition for defining a neurologic syndrome as paraneoplastic.

Clinical experience suggests that finding high titers of paraneoplastic antibodies in the CSF is confirmatory evidence of PND of the central nervous system (CNS). If an antibody is found, but is one not usually associated with the particular neurologic syndrome, then other causes for the neurologic dysfunction should be considered. Similarly, if the detected cancer is not the histologic type typically found in association with the antibody (eg, anti-Yo with lung cancer rather than breast or ovarian cancer), a second neoplasm should be suspected.¹¹

There is a group of antibodies that are associated with neurologic syndromes both in the presence and absence of cancer (Table 3). Identifying these antibodies is useful for two reasons. First, if present they alert the physician to consider an underlying cancer. Second, most of these antibodies are against ion channels or receptors expressed on the cell surface and are directly pathogenic. Disorders associated with these antibodies are therefore susceptible to treatment with immunotherapies aimed at decreasing antibody titers. However, these antibodies are not invariably associated with cancer and should not be considered as markers of PND.¹²

General clinical characteristics of classic PND

Encephalomyelitis

As the name suggests, patients with paraneoplastic encephalomyelitis (PEM) develop multifocal dysfunctions of the nervous system resulting in several syndromes that may occur in isolation or in various combinations.^{13,14} These include limbic encephalitis, cerebellar degeneration, brainstem encephalitis, myelitis, and sensory and autonomic neuropathies. As some symptoms may predominate or initially develop in isolation, formulating the

differential diagnosis can be difficult, and positive antibody studies are quite helpful. Approximately 25% of patients with PEM develop autonomic nervous system dysfunction, and respiratory or autonomic failures are frequent causes of death. The majority of patients with PEM will have a lung carcinoma, particularly SCLC, and many of these patients will have anti-Hu antibodies.¹⁴

Limbic encephalitis

The most defining characteristic of limbic encephalitis is short-term memory deficits with relative preservation of other cognitive functions.^{15–17} Partial complex temporal lobe seizures are common. Paraneoplastic limbic encephalitis is one of the few PNDs in which the neuroimaging is highly characteristic. Typical MRI findings include unilateral or bilateral abnormalities in the hippocampus, best seen on T2-weighted and FLAIR images.^{15,18} As these findings may be subtle, it is helpful to discuss the diagnosis with the radiologists to focus their attention on the limbic structures. Enhancement with gadolinium is rare, but its presence can confound interpretation of the imaging, leading to the suspicion of a neoplasm. The presence of inflammatory changes in the CSF can be very helpful to support a PND diagnosis.

A variety of paraneoplastic antibodies may be found in association with limbic encephalitis.¹⁹ Titers in the CSF are often substantially higher than titers in serum. For some immune responses, serum titers can appear negative if sensitive tests are not used; CSF is therefore preferred for testing.

Cerebellar degeneration

In an adult, the acute to subacute development of rapidly progressive cerebellar dysfunction should raise the suspicion of paraneoplastic cerebellar degeneration (PCD). Symptoms may start with dizziness, visual problems, nausea, and vomiting, and can progress within days or even hours to ataxia of gait and extremities.¹⁹ Patients are usually left with severe disabilities. Most patients with PCD do not improve, likely due to early and irreversible neuronal destruction. For patients diagnosed when symptoms are still progressing, a trial of immunosuppressive therapies may stabilize the neurologic findings.^{20–23}

Opsoclonus-myoclonus

Opsoclonus manifests as rapid, irregular, nonvoluntary and nonrhythmic movements of the eyes in horizontal and vertical directions. In adults, opsoclonus can be paraneoplastic, in which case it is often associated with myoclonus of the head, trunk, or extremities (quick, involuntary muscle jerks). The majority of these patients will have an underlying SCLC, although other cancer associations have been reported.²⁴ A subgroup of patients, usually women with breast or gynecologic cancer, develop opsoclonus-myoclonus with ataxia in association with antibodies (anti-Ri) against intraneuronal antigens. In children, paraneoplastic opsoclonus-myoclonus is a well-known complication of neuroblastoma and is sometimes referred to as the syndrome of dancing eyes and dancing feet.²⁵ Treatment of the tumor and immunotherapy in children and adults may result in substantial neurologic improvement.²⁴

Subacute sensory neuronopathy

Patients with paraneoplastic subacute sensory neuronopathy develop pain and numbness over days to weeks, often starting in one limb but eventually spreading to all four extremities and sometimes the trunk.^{13,26} When cranial nerves are affected, there can be loss of taste, facial numbness, and hearing loss. Eventually, the loss of all modalities of sensation is debilitating, with patients unable to walk or perform activities of daily living. Although a

wide variety of cancers may be associated with paraneoplastic subacute sensory neuropathy, the most common is SCLC, and many of these patients will have anti-Hu antibodies and PEM.¹⁴

Lambert-Eaton myasthenic syndrome (LEMS)

Patients with LEMS present with lower extremity weakness; increased fatigability; and difficulties walking, rising from a chair, or climbing stairs. Some patients report a brief increase in strength after a period of activity.^{4,27} At least 50% of patients have evidence of autonomic dysfunction, such as dry mouth, impotence, constipation, or impaired sweating.²⁸ While rare, respiratory muscle weakness may occur even to the point of requiring assisted ventilation.

LEMS is caused by serum antibodies against VGCCs that are expressed by the tumor, which is usually a SCLC.²⁹ These antibodies interfere with the release of acetylcholine and neuromuscular transmission. Removal of the antibodies with intravenous immunoglobulins (IVIg) or plasma exchange, and successful treatment of the tumor, results in improvement of symptoms. Drugs that increase the release of acetylcholine (eg, 3,4-diaminopyridine) and immunotherapy with azathioprine are useful for long-term treatment.³⁰

Paraneoplastic visual syndromes

Most visual disturbances in patients with cancer are related to metastatic infiltration of the optic nerves or neurotoxicity from chemotherapy and radiation therapy.^{31–33} There are two well-described paraneoplastic retinopathies, each with distinct clinical, electrophysiologic, and pathologic characteristics and immunologic associations.³⁴ Patients with cancer-associated retinopathy develop acute or subacute, often monocular visual loss that progresses to involve both eyes over days or weeks.^{35,36} Initial symptoms include photosensitivity, light-induced glare, color vision deficits, intermittent visual obscurations, and central or ring-like loss of vision.

For most patients, the underlying tumor is a SCLC, but there have been case reports associated with breast or gynecologic cancers. Melanoma-associated retinopathy has been described in patients with metastatic cutaneous melanoma. These patients present with acute visual loss years or months after the diagnosis of the metastatic disease.³⁷

Uveitis and optic neuritis may occur in the context of PEM and can be the first symptom presentation of this disorder. Patients usually have CV2/CRMP5 antibodies and SCLC.^{14,38}

Treatment

The first goal of therapy for PND is the identification and treatment of the tumor.¹⁴ Early intervention offers the best chance of neurologic stabilization or improvement. In general, PNDs affecting the peripheral nervous system are more likely to improve. For those PNDs of the peripheral nervous system associated with antibodies that are pathogenic (eg, LEMS, myasthenia gravis), IgG (antibody)-depleting therapies and immunosuppressants are often effective. For other immune-associated PNDs of the peripheral nerves or muscle, immunosuppressive therapies may be helpful. Some disorders, such as the neuropathy associated with osteosclerotic myeloma, are highly responsive to successful treatment of the tumor.³⁹

The PNDs that affect the CNS are more refractory to treatment. This is likely due to irreversible neuronal damage from the T-cell-mediated immune response that occurs early in the course of the disease.^{40,41} There are several important exceptions including limbic encephalitis (associated with anti-Ma and anti-NMDA antibodies, among others) and

opsoclonus-myooclonus.^{24,42,43} For these disorders, even when symptoms are severe, there can be remarkable recovery, and aggressive evaluations for a tumor and treatment with immunotherapies are warranted.

Although there has been concern that immunosuppression in cancer patients could favor tumor growth, there are no data to support this.⁴⁴ For patients with cancer who are also receiving chemotherapy or other antitumor treatments, there is also the concern that the addition of some immunosuppressants may result in significant toxicity. Experience demonstrates that corticosteroids, IVIg, and plasma exchange are well tolerated by most cancer patients who are also receiving chemotherapy.²³ Patients with progressive PND who have not responded to these immunotherapies, and who are not receiving chemotherapy or receiving antitumor regimens that allow for additional therapy, can be considered for more aggressive immunosuppression such as cyclophosphamide, tacrolimus (Prograf), cyclosporine, or rituximab (Rituxan).²²

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TABLE 1

Classic and nonclassic paraneoplastic neurologic syndromes

Most affected area of the nervous system	Classic	Nonclassic
Brain and/or spinal cord	<ul style="list-style-type: none"> ▪ Encephalomyelitis ▪ Limbic encephalitis ▪ Cerebellar degeneration ▪ Opsoclonus-myoclonus 	<ul style="list-style-type: none"> ▪ Brainstem encephalitis ▪ Stiff-person syndrome ▪ Necrotizing myelopathy ▪ Motor neuron disease
Peripheral nerves/spinal cord sensory neurons	<ul style="list-style-type: none"> ▪ Subacute sensory neuronopathy ▪ Gastrointestinal paresis or pseudo-obstruction 	<ul style="list-style-type: none"> ▪ Guillain-Barré syndrome ▪ Subacute and chronic mixed sensory-motor neuropathies ▪ Neuropathy associated with plasma cell dyscrasias and lymphoma ▪ Vasculitis of nerve ▪ Pure autonomic neuropathy
Muscle and neuromuscular junction	<ul style="list-style-type: none"> ▪ Dermatomyositis ▪ Lambert-Eaton myasthenic syndrome 	<ul style="list-style-type: none"> ▪ Acute necrotizing myopathy ▪ Polymyositis ▪ Vasculitis of muscle
Eye	<ul style="list-style-type: none"> ▪ Cancer- or melanoma-associated retinopathy 	<ul style="list-style-type: none"> ▪ Optic neuritis

TABLE 2

Paraneoplastic antibodies and associated neurologic syndromes and cancers

Antibody	Neurologic syndrome	Commonly associated cancers
Anti-Hu	Encephalomyelitis, sensory neuropathy	SCLC, other
Anti-Yo	Cerebellar degeneration	Gynecologic, breast
Anti-Ri	Cerebellar ataxia, opsoclonus	Breast, gynecologic
Anti-Tr	Cerebellar degeneration	Hodgkin's lymphoma
Anti-CV2/CRMP5	Encephalomyelitis, uveitis, neuropathy	SCLC, thymoma, other
Anti-Ma proteins	Limbic, ^a brainstem, ^b or diencephalic ^c encephalitis	Testicular germ-cell tumors, other
Anti-amphiphysin	Stiff-man syndrome, encephalomyelitis	Breast, SCLC

SCLC = small-cell lung cancer; CRMP = collapsing response-mediator protein

^aPredominant short-term memory deficits with relative preservation of other cognitive functions; partial complex temporal lobe seizures^bSymptoms may include vertigo, eye-movement abnormalities, ataxia, dysarthria, dysphagia, and respiratory insufficiency, among others.^cSymptoms may include excessive daytime sleepiness, narcolepsy-cataplexy, hyper- or hypothermia, and hypothalamic-pituitary endocrine dysfunction, among others.

TABLE 3

Antibodies associated with neurologic syndromes that may or may not occur with cancer

Antibody ^a	Neurologic syndrome	Commonly associated cancers
Anti-VGKC	Neuromyotonia, limbic encephalitis	Thymoma, SCLC
Anti-VGCC	LEMS, cerebellar degeneration	SCLC
Anti-AChR (muscle)	Myasthenia gravis	Thymoma
Anti-AChR (neuronal)	Autonomic neuropathy	SCLC
Anti-NMDAR	Anti-NMDAR encephalitis	Teratoma
Anti-AMPA	Limbic encephalitis	SCLC, thymoma, breast
Anti-GAD	Stiff-person, cerebellar syndromes	Thymoma

VGKC = voltage-gated potassium channel; SCLC = small-cell lung cancer; VGCC = voltage-gated calcium channel; LEMS = Lambert-Eaton myasthenic syndrome; AChR = acetylcholine receptor; NMDAR = *N*-methyl-D-aspartate receptor; AMPAR = α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; GAD = glutamic acid decarboxylase

^a All but anti-GAD are cell-surface antigens.