＜特別講演 1＞

Paraneoplastic Disorders of the Nervous System

Josep Dalmau, MD, PhD

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Introduction

Paraneoplastic neurologic disorders (PND) refer to an extensive group of syndromes that can affect any part of the nervous system by mechanisms that are mostly immune mediated (Table 1). PND are more frequent than previously considered, with an incidence that varies with tumor type. The tumors more frequently involved are small-cell lung cancer (SCLC, ～3% of patients develop PND), thymoma (15%), and the plasma cell dyscrasias associated with malignant monoclonal gammopathies (～5-15%). For solid tumors other than SCLC the incidence of PND is less than 1%.

In 60% of patients, symptoms of PND precede the tumor diagnosis. The majority of these patients are first seen by neurologists who should be aware that prompt diagnosis and treatment of the tumor along with immunotherapy may stabilize or improve the PND.

Pathogenesis

Many PND of the central nervous system (CNS) occur in association with antibodies against intraneuronal antigens expressed by the underlying cancer (paraneoplastic or onconeuronal antibodies; Table 2). The identification of infiltrates of T-cells in the patients' CNS, and the lack of success modelling the disease by transfer of antibodies have suggested that T-cells play an important role in the pathogenesis of these syndromes. Studies show that in addition to paraneoplastic antibodies, T-cells specific for the paraneoplastic antigens are detectable in the patients' blood or CSF. It is believed that after crossing the blood-brain barrier these T-cells are involved in the neuronal injury. It remains uncertain whether the T-cells are effective against the tumor, and if so whether the anti-tumor effect is sustained enough to be clinically efficient.

Some antibodies appear to have a direct pathogenic role in causing PND. These antibodies usually react with cell surface antigens and until recently were considered predominantly involved in syndromes of the neuromuscular junction or peripheral nerves. For most of these immune responses the associated symptoms and electrophysiological abnormalities have been reproduced in animal models. The best characterized antibodies to cell surface antigens are shown in italics in Table 2.

General Diagnostic Approach

The diagnosis of PND is usually based on the recognition of the neurological syndrome, the demonstration of the associated cancer, and the detection of serum and CSF paraneoplastic antibodies.

Associated Cancer

PND usually develop at early stages of cancer and therefore, the tumor may be difficult to demonstrate. The combination of CT of the chest, abdomen and pelvis, and F-18 fluorodeoxyglucose whole body positron emission tomography (FDG-PET) is useful in revealing occult neoplasms. The type of syndrome and paraneoplastic antibody may suggest a specific underlying tumor and direct to the use of additional tests, such as mammogram or ultrasound of the pelvis or testes.

All patients with a neuropathy of unclear etiology should be examined for the presence of a monoclonal gammopathy in the serum and urine, and if positive undergo a skeletal survey and bone marrow biopsy; these studies may uncover a malignant plasma cell dyscrasia, amyloidosis, or B-cell lymphoma.

Paraneoplastic antibodies

The term "paraneoplastic antibodies" is applied to antibodies which presence serves as a marker of the paraneoplastic origin of a neurological syndrome. Detection of "well-characterized antibodies" (Table 2) strongly supports the diagnosis of PND even if no tumor is found. "Partially-characterized antibodies" are those for which limited clinical experience is available or the target antigens are unknown.

Division Neuro-Oncology, Department of Neurology, 3 W. Gates University of Pennsylvania〔3400 Spruce Street Philadelphia, PA 19104〕

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Table 1 Paraneoplastic syndromes of the nervous system

Location of pathological findings	Paraneoplastic Neurological Disorders	
	Classical	Non-classical
Brain, cranial nerves and retina	Cerebellar degeneration Limbic encephalitis Encephalomyelitis Opsoclonus-myoclonus	Brainstem encephalitis Optic neuritis Cancer-associated retinopathy Melanoma-associated retinopathy
Spinal cord*		Stiff-person syndrome Myelitis Necrotizing myelopathy Motor neuron syndromes
Neuromuscular junction	Lambert-Eaton myasthenic syndrome	Myasthenia gravis
Peripheral nerves or muscle*	Sensory neuronopathy Intestinal pseudoobstruction Dermatomyositis	Sensorimotor neuropathy Neuropathy and paraproteinemia Neuropathy with vasculitis Acquired neuromyotonia Autonomic neuropathies Polymyositis Acute necrotizing myopathy

*Reviewed in references[2) 3)]

Several antibodies, including P/Q type VGCC; VGKC; nicotinic or ganglionic AChR, and NMDA receptor antibodies can be detected in both, the paraneoplastic and non-paraneoplastic form of the associated disorder.

Diagnostic Criteria of PND

The information provided by the type of neurological syndrome, detection of cancer, and presence or absence of paraneoplastic antibodies has been used to define specific diagnostic criteria.

Frequent Paraneoplastic Syndromes

Paraneoplastic Encephalomyelitis (PEM)

PEM refers to an immune mediated inflammatory disorder that can affect any part of the CNS, dorsal root ganglia, and autonomic nerves. The main areas involved include the hippocampus (limbic encephalitis), the Purkinje cells of the cerebellum (cerebellar degeneration), the lower brainstem (brainstem encephalitis), dorsal root ganglia (sensory neuronopathy), spinal cord (myelitis), and the sympathetic or parasympathetic ganglia and nerves (orthostatic hypotension, gastrointestinal paresis or pseudo-obstruction, cardiac arrhythmia, erectile dysfunction, abnormal pupillary responses to light). Less frequently, patients may develop discrete focal cortical encephalitis, sometimes presenting as epilepsia partialis continua.

Symptoms of PEM develop rapidly and progress over weeks or months until stabilization or death. The CSF is almost always abnormal with mild to moderate lymphocytic pleocytosis, increased protein concentration, normal glucose concentration, and oligoclonal bands or increased IgG index.

Several antibodies assist in the diagnosis of PEM and the underlying neoplasm (Table 2). The management of PEM is based in prompt treatment of the tumor along with immunosuppression focused in the T-cell response.

Limbic Encephalitis

Patients with limbic encephalitis develop short-term memory loss, seizures, confusion, irritability, depression, sleeping problems, or psychiatric symptoms. The MRI often shows medial temporal lobe FLAIR or T2 abnormalities. FDG-PET may show hyperactivity in regions that are normal in the MRI. EEG often demonstrates uni- or bilateral temporal lobe epileptic discharges, or slow background activity. The antibodies and tumors more frequently involved are shown in Table 2. Ma2 antibodies also occur in some patients with diencephalic and brainstem encephalitis; the later can cause severe hypokinesis.

The response of paraneoplastic limbic encephalitis to treatment is difficult to predict; some patients show improvement if the tumor is treated promptly and, sometimes, with corticosteroids and IVIg, while others with similar symptoms and antibodies are refractory to treatment. There is some evidence that patients without paraneoplastic antibodies or young patients with anti-Ma2 antibodies are more likely to improve than patients with anti-Hu or CV2/CRMP5 antibodies.

Limbic encephalitis associated with VGKC antibodies has recently been described. In this disorder hyponatremia is frequent, and patients may also have accompanying hallucinations, autonomic and peripheral nerve dysfunction (neuro-

Table 2 Antibodies, paraneoplastic syndromes, and associated cancers

WELL-CHARACTERIZED PARANEOPLASTIC ANTIBODIES*		
Antibody	Syndrome	Associated Cancers
Anti-Hu (ANNA-1)	PEM including cortical, limbic, brainstem encephalitis, PCD, myelitis, PSN, autonomic dysfunction	SCLC, other
Anti-Yo (PCA-1)	PCD	Gynecological, breast
Anti-Ri (ANNA-2)	PCD, brainstem encephalitis, opsoclonus-myoclonus	Breast, gynecological, SCLC
Anti-CV2/CRMP5	PEM, PCD, chorea, uveitis, optic neuritis, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins[a]	Limbic, hypothalamic, brainstem encephalitis (infrequently PCD).	Germ-cell tumors of testis, non-SCLC, other solid tumors
Anti-amphiphysin	Stiff-person syndrome, PEM, limbic encephalitis, myelopathy	SCLC, breast
PARTIALLY-CHARACTERIZED PARANEOPLASTIC ANTIBODIES*		
Anti-Tr	PCD	Hodgkin's lymphoma
Anti-Zic 4	PCD	SCLC
mGluR1	PCD	Hodgkin's lymphoma
ANNA3	Various PND of the CNS	SCLC
PCA2	Various PND of the CNS	SCLC
ANTIBODIES THAT OCCUR WITH AND WITHOUT CANCER ASSOCIATION		
Anti-NR1/NR2 of NMDA receptor	Characteristic encephalitis [b]	Teratoma (usually in the ovary)
Anti-VGKC	Limbic encephalitis, PNH (neuromyotonia), other	Thymoma, SCLC, other
Anti-VGCC	LEMS, PCD	SCLC
Anti-AChR	MG	Thymoma
Anti-nAChR	Subacute pandysautonomia	SCLC, others
Anti-GAD	Stiff-person syndrome, cerebellar ataxia, limbic encephalitis, other	Thymoma, other

Italics indicate antibodies that react with cell surface antigens

*Well-characterized antibodies are those directed against antigens whose molecular identity is known or that have been identified by several investigators.

(a) The main antigen is Ma2. In addition, patients may develop antibodies to Ma1.

(b) Anti-NMDA receptor encephalitis: prominent psychiatric symptoms, memory loss, decreased level of consciousness with frequent hypoventilation, autonomic instability, and dyskinesias

PEM; paraneoplastic encephalomyelitis; PCD: paraneoplastic cerebellar degeneration; PSN: paraneoplastic sensory neuronopathy; SCLC: small-cell lung cancer; PND: paraneoplastic disorder; mGluR1: metabotropic glutamate receptor 1; NMDA: N-methyl-D-aspartate; PNH: peripheral nerve hyperexcitability; VGKC: voltage-gated potassium channels; VGCC: voltage-gated calcium channels; AChR: acetylcholine receptor; nAChR: neuronal AChR; LEMS: Lambert-Eaton myasthenic syndrome; MG: myasthenia gravis; GAD: glutamic acid decarboxylase.

myotonia) and rapid eye movement sleep behavior abnormalities (Morvan's syndrome). The CSF of patients with syndromes related to VGKC antibodies is usually normal or shows milder changes than that of patients with classical paraneoplastic antibodies. Although VGKC antibodies have been described in the "non-paraneoplastic" category, in practice, patients should be examined for thymoma and SCLC because these tumors have been identified in ~20% of cases. In 70-80% of patients with limbic encephalitis and VGKC antibodies, the use of corticosteroids, IVIg or plasma exchange result in significant improvement.

There is an emerging group of encephalitides that may present with predominant psychiatric dysfunction or as a clinical picture of limbic encephalopathy in association with antibodies to cell membrane antigens. One of the autoantigens is the NMDA receptor, but there are other cell membrane antigens pending characterization. Despite the severity of the symptoms these disorders often respond to removal of the tumor and corticosteroids, plasma exchange, IVIg, rituximab or cyclophosphamide.

Encephalitis associated with NMDA receptor antibodies

A recently described group of patients develop subacute psychiatric symptoms, seizures, short-term memory deficits, decreased level of consciousness, dyskinesias, autonomic dys-

function, and hypoventilation, usually requiring ventilatory support. The CSF usually shows pleocytosis, increased protein concentration and oligoclonal bands or elevated IgG index. Patients may require intensive care support for several weeks or months. An immature or mature ovarian teratoma (or "dermoid cyst") is found in 65% of patients; it can be overlooked if only FDG-PET is used for cancer detection. The disorder can also affect men; some patients have teratoma of the testis. Resection of the tumor, corticosteroids, IVIg or plasma exchange usually associates with improvement. Patients who do not respond to these treatments often respond to rituximab and/or cyclophosphamide. The serum and CSF of these patients contain antibodies that react with NR1/NR2 heteromers of the NMDA receptor.

Paraneoplastic Cerebellar Degeneration (PCD)

Patients with PCD usually present with dizziness, vertigo, oscillopsia, gait unsteadiness that in a few days or weeks evolve to severe gait and limb ataxia. Other clinical features include dysarthria, dysphagia, diplopia, and predominant downbeating nystagmus. The CSF usually shows the abnormalities common to most paraneoplastic syndromes of the CNS. MRI of the brain is often normal at symptom presentation, and shows progressive cerebellar atrophy as the disease evolves.

Cerebellar symptoms may occur in association with any of the paraneoplastic antibodies shown in Table 2. The tumors more frequently associated with PCD are lung, ovary, breast cancer and lymphoma. A few antibodies (anti-Yo, anti-Tr) associate with dominant cerebellar symptoms without significant involvement of other areas of the nervous system. Patients with PCD and SCLC should be evaluated for motor weakness because some of these patients may have LEMS.

As occurs with other PND, 30-40% of patients with PCD do not harbour antineuronal antibodies. In these patients the differential diagnosis is extensive. PCD is one of the most difficult syndromes to treat, but prompt diagnosis and treatment of the tumor and immunotherapy may stabilize the disorder or prevent further involvement of other areas of the nervous system.

Opsoclonus-Myoclonus (OM)

Opsoclonus is a disorder of eye motility with involuntary, multidirectional, chaotic, conjugate saccades. It almost always associates with myoclonus of the trunk and limbs, and sometimes with truncal or limb ataxia. The pathological substrate of OM has not been firmly established. Recent pathological and functional MRI studies suggest a disinhibition of the fastigial nucleus of the cerebellum as a possible substrate of the disorder.

In adults the tumors more frequently involved are SCLC, gynecological and breast cancers. In children, OM is usually accompanied by hypotonia, irritability, behavioural change, refusal to walk or sit, sleep dysfunction, episodes of rage, and psychomotor retardation. The underlying tumor is a neuroblastoma.

Most patients with paraneoplastic OM do not have paraneoplastic antibodies. An exception is the anti-Ri antibody that identifies a subgroup of patients with ataxia, breast or gynecological cancers, and less frequently SCLC.

Paraneoplastic OM may respond to IgG-depleting strategies (IVIg or plasma exchange and corticosteroids) and treatment of the tumor; improvement is rare if the tumor is not treated. Children with paraneoplastic OM may respond to treatment of the tumor, prednisone, ACTH, plasma exchange, IVIg, or rituximab. The use of trazodone improves the episodes of rage.

Paraneoplastic Sensory Neuronopathy (PSN)

PSN is characterized by progressive numbness and often painful dysesthesias involving the limbs, trunk, and less frequently the cranial nerves causing face numbness or sensorineural hearing loss. The symptom presentation is frequently asymmetric, associated with decreased or abolished reflexes, and relative preservation of strength. All types of sensation can be affected, but loss of proprioception is often predominant. As a result, patients develop sensory ataxia and pseudoathetoid movements of the extremities demonstrated when the patient closes the eyes or is distracted during the examination. PSN frequently associates with PEM, particularly in patients with SCLC. These patients almost always harbour anti-Hu antibodies.

Prompt treatment of patients with corticosteroids and IVIg (along with treatment of the tumor) may result in stabilization or mild improvement of the dorsal root ganglia dysfunction, sometimes confirmed with improvement of electrophysiological studies.

Lambert-Eaton Myasthenic Syndrome (LEMS)

LEMS results from an antibody-mediated attack against the P/Q type VGCC located at the presynaptic level of the neuromuscular junction. This interferes with the release of acethylcholine and results in muscle weakness and fatigability. LEMS should be suspected in patients with proximal weakness, dry mouth, and decreased or absent reflexes, particularly if the patient is known to have SCLC or a history of smoking. Signs of autonomic dysfunction may include orthostatic hypotension, erectile dysfunction and blurred vision due to abnormal pupillary responses. Mild muscle ache and distal paresthesias are common. Cranial nerve involvement is frequent, but mild and transient.

Approximately 60% of patients with LEMS have an underlying neoplasm, usually SCLC. Paraneoplastic LEMS may associate with PCD or PEM. Treatment of the tumor and medi-

cation that enhance acetylcholine release (3,4-diaminopyridine, or combination of pyridostigmine and guanidine) are usually effective. IVIg and plasma exchange improve symptoms within 2-4 weeks but the benefit is transient. Long-term immunotherapy with prednisone or azathioprine is an alternative for patients who do not improve with 3,4-diaminopyridine.

The recent discovery that a SCLC-related protein, called SOX, is the antigen recognized by AGNA (antiglial nuclear antibody) and these antibodies occur in 64% of patients with cancer-associated LEMS provide a potential test for recognizing LEMS of paraneoplastic etiology. SOX antibodies appear to have the same diagnostic value in patients with limbic encephalitis and VGKC antibodies or other neuronal cell surface antigens.

Recommended Readings

1) Graus F, Delattre JY, Antoine JC, et al: Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004; 75: 1135—1140
2) Rudnicki SA, Dalmau J: Paraneoplastic syndromes of the peripheral nerves. Curr Opin Neurol 2005; 18: 598—603
3) Antoine JC, Camdessanche JP: Peripheral nervous system involvement in patients with cancer. Lancet Neurol 2007; 6: 75—86
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5) Tuzun E, Dalmau J: Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist 2007; 13: 261—271
6) Sabater L, Titulaer M, Saiz A, et al: SOX1 antibodies are markers of paraneoplastic Lambert-Eaton myasthenic syndrome. Neurology 2008; 70: 924—928