Paraneoplastic disorders of the nervous system are important to the practicing oncologist, because these syndromes, although uncommon, produce significant neurologic dysfunction and disability. The neurologic disorder may be the first manifestation of an unrecognized systemic malignancy, and appropriate diagnosis of the paraneoplastic disorder can lead to a focused search for an underlying cancer. Paraneoplastic disorders may involve any component of the central or peripheral nervous system, and diagnosis requires careful neurologic assessment. The diagnosis is made by recognition of clinical neurologic syndromes and the use of selected laboratory studies as indicated by the clinical picture. Over the past 10 years, the application of molecular biologic techniques to the study of these disorders has elucidated much about the mechanisms that cause neurologic injury. In most cases, disordered humoral and cellular immunity has been demonstrated, and the role of novel targets for autoimmune attack is being clarified. For some paraneoplastic disorders, treatment of the underlying tumor may lead to improvement of the neurologic disorder. For others, various forms of immunosuppressive therapy may be indicated. Unfortunately, for several of the more common paraneoplastic syndromes such as paraneoplastic cerebellar degeneration or limbic encephalitis, treatment is still unsatisfactory, and further research into the exact pathophysiology is clearly needed. [ONCOLOGY 16:1539-1556, 2002]

*Neurologic diseases are defined as paraneoplastic when they occur with increased frequency in patients with cancer and are not related to a direct effect of the tumor, infection, metabolic abnormalities, or toxicity of therapy.*[1,2] Autoantibodies and evidence of cellular autoimmunity directed against neuronal, glial, or muscle cell antigens have been identified in several paraneoplastic neurologic disorders.[3,4] Over the past 4 decades, investigators have identified and reported these disorders using a variety of names. This review follows the nosology employed by Posner.[2]

Paraneoplastic disorders are rare, but accurate diagnosis is important. In patients without a known malignancy, correct diagnosis may lead to the discovery and early treatment of the underlying malignancy. Effective treatment may improve the patient’s neurologic dysfunction and quality of life. In addition, proper diagnosis of a paraneoplastic disorder can spare the patient an extensive and expensive search for alternative etiologies of the neurologic dysfunction.

Paraneoplastic disorders are diagnosed by recognition of stereotypic clinical syndromes and, when appropriate, confirmatory laboratory studies demonstrating evidence of autoimmunity. Autoantibodies against specific neural antigens characterize several neurologic disorders ([Figure 1](#)).[3] In some disorders, eg, Lambert-Eaton myasthenic syndrome associated with small-cell lung cancer (SCLC),[5] or myasthenia gravis associated with thymoma,[6] the antibodies are clearly important to the pathogenesis of the disease, and immunosuppression is clearly effective.[7,8] In other disorders, such as encephalomyeloneuritis associated with SCLC, the role of the antibody response in producing neurologic dysfunction is less clear.[8-10]

**Subacute Sensory Neuronopathy-Encephalomyeloneuritis**

Most frequently associated with SCLC, subacute sensory neuronopathy-encephalomyeloneuritis (SSN-EMN) may affect multiple sites within the central and peripheral nervous system.[11] When SSN-EMN occurs in patients with SCLC, antibodies called anti-Hu are usually present in the serum ([Figure 1](#)); high-titer antibodies to the Hu antigen are almost never seen in patients without SCLC.[11] Diagnosis of SSN-EMN and documentation of anti-Hu antibody should lead to a search for SCLC, which is often localized at the time of diagnosis of the neurologic disorder. Low-titer anti-Hu antibodies have been documented in patients with SCLC and no neurologic disease.[12] and the association with localized SCLC suggests that anti-Hu antibodies are a marker for systemic immune
suppression of tumor progression.

Various Presentations

The range of presentations and extent of neurologic involvement in patients with paraneoplastic disorders associated with anti-Hu antibodies is quite broad. One presentation is a pure sensory neuropathy.[13] The disorder progresses relentlessly over days to weeks, and sensory nerve action potentials are lost.[14] The cerebrospinal fluid usually demonstrates increased protein concentration and a lymphocytic pleocytosis. In SSN associated with anti-Hu antibody (Figure 2), the dorsal root ganglia show lymphocytic infiltration and loss of neurons.[15] At postmortem examination, inflammatory changes in other regions of the nervous system have been seen in approximately half of the SSN patients studied.

Most cases of SSN are associated with other autoimmune disorders rather than cancer, and anti-Hu antibodies are absent. The association of anti-Hu antibodies with Sjögren’s syndrome is probably spurious.[16] Immunosuppressive therapy is usually ineffective,[17] although spontaneous remission may occur. Treatment of the underlying SCLC may ameliorate the neurologic dysfunction,[18] and treatment of Hodgkin’s disease with chemotherapy resulted in improvement in one patient.[18]

Limbic Encephalitis

The clinical, radiologic, and immunobiologic features of limbic encephalitis have been described in two recent analyses encompassing 250 patients.[19,20] Limbic encephalitis may be mistaken for herpes simplex encephalitis, because its symptoms also include memory disturbance, agitation, and seizures. Magnetic resonance imaging (MRI) scans may show mesial temporal contrast enhancement or T2 signal hyperintensities.[21] The cerebrospinal fluid shows increased protein concentration and a lymphocytic pleocytosis. Patients may exhibit symptoms of SSN, or there may be involvement of the brain stem or spinal cord. Biopsy of the temporal lobe may reveal perivascular lymphocytic infiltrates. In autopsy specimens, neuronal loss and gliosis are most prominent in the limbic and insular cortex.[19]

Molecular characterization of target antigens divides this syndrome into distinguishable diseases. Most cases of limbic encephalitis are associated with SCLC and the presence of anti-Hu antibodies in the serum and cerebrospinal fluid.[19,20] Testicular cancer patients with limbic encephalitis harbor a different antibody.[22] In a series of 13 testicular cancer patients with limbic encephalitis, 10 harbored antibodies against a novel onconeural antigen named Ma2—a 40-kd protein shared by the testis and normal brain that is widely expressed in the normal human central nervous system (CNS) as well as dorsal root ganglia. A related onconeural antigen, Ma1, is associated with cerebellar or brain-stem dysfunction in patients with lung, breast, parotid gland, or colon cancer.[23]

Treatment Options

Limbic encephalitis may be one of the more treatable CNS paraneoplastic disorders.[19,20] Over 40% of patients followed for more than 8 months in a recent series demonstrated some neurologic improvement. Treatment of the underlying tumor appears to be more effective than immunosuppressive therapy. This experience adds to earlier reports of improvement after successful treatment of an underlying lung cancer.[24]

The distinction between anti-Ma2- and anti-Hu-associated limbic encephalitis is important, because patients with anti-Ma2-associated limbic encephalitis have a better prognosis. Orchiectomy and aggressive treatment of residual disease have proven to be most effective as therapy for the anti-Ma2-associated syndrome,[22] whereas immunosuppression has been less successful. One patient, however, did improve after treatment with corticosteroids and intravenous (IV) immunoglobulin (Ig) G.

Patients with limbic encephalitis should be tested for anti-Hu antibodies; male patients should undergo examination of the testes and be tested for anti-Ma2 antibodies. Detection of anti-Hu or anti-Ma antibodies indicates the likely presence of SCLC or testicular cancer, respectively. In rare
instances, small-cell cancers of other organs, including poorly differentiated small cell carcinoma of the prostate, have been diagnosed as the only systemic cancer in patients with limbic encephalitis and anti-Hu antibodies.[11]

Brain-stem encephalitis and myelitis usually occur together and in association with limbic encephalitis.[25] MRI scanning must exclude metastatic tumor. Most cases are associated with anti-Hu antibodies, although other autoantibodies may be present. Brain-stem encephalitis and myelitis usually progress relentlessly and rapidly.

**Autonomic Neuropathy**

A pure paraneoplastic, autonomic neuropathy is rare, but approximately 25% of patients with anti-Hu syndrome and SSN-EMN manifest autonomic dysfunction.[19] Progressive paraneoplastic autonomic failure is rarely the first symptom of an occult malignancy. Bladder dysfunction, bowel immotility and obstruction, and postural hypotension may be disabling.[26] The disorder is usually associated with SCLC and autoantibodies that react with neurons in the myenteric plexus.[26] In a series from the Mayo Clinic, 42% of patients with subacute autonomic neuropathy demonstrated antibodies against the nicotinic acetylcholine receptor.[27,28]

**Progressive Cerebellar Degeneration**

Subacute cerebellar degeneration in an adult without a family history of cerebellar disease demands investigation to exclude underlying tumor.[2] Posner[2] has classified progressive cerebellar degeneration into subcategories based on the underlying tumor, associated clinical features, and presence of specific associated autoantibodies.

**Symptoms**

Patients usually first complain of having difficulty walking, which progresses over weeks to months. Diplopia and vertigo may be early symptoms. Loss of dexterity, dysarthria, and oscillopsia associated with nystagmus appear, and the patient usually becomes incapacitated.[29] Subtle motor system or cognitive dysfunction may occur.[30] Imaging studies may show diffuse cerebellar atrophy,[31] but contrast-enhancing lesions or lesions with mass effect are not associated with progressive cerebellar degeneration.

During the early phase of the disorder, the cerebrospinal fluid usually shows a lymphocytic pleocytosis and mildly elevated protein concentration.[30] Oligoclonal bands have been reported.[29] The most common pathologic finding is diffuse, extensive loss of Purkinje cells in the cerebellum.[29] Inflammatory changes are frequently minimal in the Purkinje cell layer and more prominent in the surrounding white matter, leptomeninges, or the region of the dentate nucleus.

**Associated Etiologies**

Anti-Yo progressive cerebellar degeneration is most commonly associated with ovarian or breast carcinoma ([Figures 1](#) and [3](#)), and patients are almost exclusively women. Frequently, the neurologic disorder antedates discovery of the tumor. The Yo antigen is one of a family of three cerebellar-degeneration-related antigens identified by expression cloning.[32-34] Only Yo, or CDR2, is transcribed in human tumors.

The disorder is subacute at onset and usually progressive. Most patients develop downbeating nystagmus, oscillopsia, and diplopia. Patients become 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. Early recognition of the syndrome may allow more effective attempts at immunosuppressive therapy.

Patients with progressive cerebellar degeneration and Hodgkin's disease are predominantly male, and these men tend to be younger than females with anti-Yo progressive cerebellar degeneration.[35] Frequently, patients who have already been treated for Hodgkin’s disease develop...
the disorder. Antibodies against a novel onconeural antigen named Tr have been found in Hodgkin’s disease patients with this syndrome.[36,37] However, progressive cerebellar degeneration associated with Hodgkin’s disease has a better prognosis than the anti-Yo-associated syndrome.[35] Spontaneous improvement occurred in 15% of cases in one series, and one patient improved significantly with effective treatment of Hodgkin’s disease.[36] As the patient responded to treatment, the anti-Tr antibody declined 10-fold in serum and disappeared from the cerebrospinal fluid.[37]

Antibody-negative progressive cerebellar degeneration may develop in conjunction with Lambert-Eaton myasthenic syndrome. Approximately 30 cases have been reported; in some, no tumor was identified.[38] The most common associated tumor is SCLC. The progressive cerebellar degeneration may not remit, even as the myasthenic syndrome responds to immunosuppression.

Approximately 15% of patients with anti-Hu antibodies develop progressive cerebellar degeneration as the first manifestation of disease. These patients often present with signs suggesting multisystem involvement. Identification of the anti-Hu antibody directs the search for SCLC.

Progressive cerebellar degeneration has been associated with a variety of other solid tumors and with myelogenous leukemia and monoclonal gammopathy.[2] It is unclear whether these cases are causally related to the associated tumors.

Paraneoplastic Visual Loss

Paraneoplastic disorders are a rare cause of visual loss in cancer patients. Paraneoplastic visual syndromes may be identified by clinical history, ophthalmologic examination, retinal electrophysiologic studies, and the presence or absence of autoantibodies.[39] Retinal disorders are the most common type of this problem. Within this class, photoreceptor degenerations are the best characterized.[40]

Patients with photoreceptor degeneration commonly experience night blindness, photopsias, and blurred vision. If cones are involved, loss of color perception may occur. Electroretinograms are abnormal and ophthalmoscopic examination may reveal retinal arteriolar attenuation.[40]

Several different autoantibodies have been described in association with photoreceptor degeneration, but the most common is the anti-cancer-associated retinopathy (CAR) antigen. The target antigen is recoverin, a calcium-binding molecule involved in the transduction of light signaling in vertebrate photoreceptors.[41] The majority of patients with anti-CAR antigen have cancer, usually SCLC, but a similar syndrome has been reported in patients with no detectable cancer.[42] Usually, the visual loss is progressive and ultimately results in blindness, but occasionally patients have responded to high-dose corticosteroids, plasmapheresis, or IV IgG.[42]

In addition to CAR-related antibody, antibodies directed against a variety of retinal antigens including neurofilaments[43] have been reported in patients with photoreceptor degeneration. Most of these patients have SCLC, non-small-cell lung cancer (NSCLC), or breast cancer. Some patients with anti-Hu syndrome develop retinal photoreceptor degeneration. Treatment of the underlying tumor usually does not modify the course of the visual syndrome.

Progressive visual loss with retinal pigmentary abnormalities has been separated into several syndromes. These disorders are most commonly associated with melanoma or adenocarcinomas of the gut[39] and have distinctive ophthalmoscopic appearances. Acquired night blindness has been reported in association with melanoma.[39] Isolated cone dystrophy has also been reported as a paraneoplastic syndrome.

Paraneoplastic Optic Neuropathies

A small number of patients present with paraneoplastic optic neuropathies.[44-47] Ophthalmoscopic examination may reveal optic disk pallor, but no retinal pigmentary changes or vascular attenuation. Optic neuropathy may be associated with anti-CV2 antibodies. These patients often have
concomitant cerebellar dysfunction and sensorimotor neuropathy.[45] Electoretinograms are normal, but visual evoked potentials are delayed. Patients do not complain of photopsia; instead, progressive scotoma related to optic nerve dysfunction develop.

Occasionally, patients with paraneoplastic optic neuropathy improve with immunosuppression.[46] In one such case, a patient with multiple myeloma and an antibody directed against an antigen in the retinal ganglion cells recovered completely after high-dose chemotherapy and stem cell transplantation obliterated the autoantibody.[47]

**Opsoclonus Myoclonus**

This disorder of ocular motility and multifocal myoclonus was first described in children with neuroblastoma. Approximately 50% of pediatric cases are paraneoplastic.[2] Because opsoclonus myoclonus antedates the discovery of neuroblastoma in many children, the search for underlying neuroblastoma is necessary in any child who develops the disorder. The peak age of onset is 18 months, and girls are preferentially afflicted. Significant neurologic dysfunction frequently persists in children with opsoclonus myoclonus and neuroblastoma.[48]

Favorable disease stage at diagnosis of the neuroblastoma correlates with a higher risk of neurologic sequelae in pediatric patients with opsoclonus myoclonus, but the presence of antineuronal antibodies does not.[49] Successful treatment of neuroblastoma may be associated with a better neurologic outcome.[48] Although antineuronal antibodies are frequently detected in children with opsoclonus myoclonus and neuroblastoma, no single antigen seems to be the common target. Antineurofilament antibodies were implicated in one pediatric case,[50] and anti-Hu antibodies in another.[51]

**Anti-Ri Antibody**

A novel antibody called anti-Ri has been reported in several adult patients with opsoclonus and truncal ataxia or other cerebellar signs (Figure 1). These cases were associated with breast or gynecologic cancers.[52] Anti-Ri antibodies recognize 55-kd and 80-kd bands on denaturing Western blots of cortical neurons. It is unclear whether the neurologic prognosis is different for antibody-negative vs anti-Ri-associated opsoclonus myoclonus. The target antigen is Nova, an RNA-binding protein; anti-Ri antibodies derived from patients recognize a region of the protein necessary for RNA interaction,[53] suggesting a mechanism for antibody-mediated toxicity.

Another etiology of opsoclonus myoclonus in adult lung cancer patients may be malnutrition and vitamin deficiency, and some patients have improved with thiamine.[2] Paraneoplastic opsoclonus myoclonus has also been associated with Hodgkin’s disease. Such patients do not have anti-Ri antibodies.[54]

**Paraneoplastic Motor Neuron Disorders**

Most cases of motor neuron disorders in cancer patients probably represent the concomitant occurrence of two common disorders in the same patient. However, paraneoplastic motor neuron disorder syndromes do occur and diagnosis is important, because patients may improve after removal of the tumor or immunosuppressive therapy.[55] Experienced neuromuscular clinicians believe that these disorders can be differentiated from amyotrophic lateral sclerosis (ALS) by clinical and electrophysiologic criteria and discourage an extensive search for occult malignancy in patients with typical ALS. However, paraneoplastic motor neuron disorders with a variable mixture of upper and lower motor neuron signs have been reported in association with both lymphoproliferative malignancies and solid tumors.[56-60]

In a series reported from Memorial Sloan-Kettering Cancer Center, patients with paraneoplastic motor neuron disorders were divided into three different groups.[57]. One group harbored anti-Hu antibodies.[58] In these patients, progressive motor neuron dysfunction is part of a more complex syndrome incorporating features of the anti-Hu syndrome. Another group of five women with primary lateral sclerosis and breast cancer did not have anti-Hu or other autoantibodies. A third group
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developed a syndrome resembling ALS and had a variety of underlying solid tumors.

Patients with Hodgkin’s disease or non-Hodgkin’s lymphoma, paraproteinemia, and a mixed upper and lower motor neuron syndrome have been reported. Lower motor neuron syndromes, as well as a mixture of lower and upper motor neuron signs, have also been reported in association with myeloproliferative disorders and paraproteinemias. A rapidly progressive, painless lower motor neuron syndrome developed in one patient with angiocentric lymphoma.

Case reports suggest that patients may improve substantially after treatment of the underlying malignancy or, less clearly, with immunosuppression. Remission of the motor neuron syndrome has been reported after nephrectomy in a patient with renal cell carcinoma and with successful treatment of lung cancer.

Posner suggested that the predominantly lower motor neuron disorder known as subacute motor neuronopathy or spinal muscular atrophy is an opportunistic viral syndrome. This syndrome has been reported in patients with Hodgkin’s disease and in those with non-Hodgkin’s lymphoma. Presentations include multifocal motor weakness and sensory complaints. The cerebrospinal fluid is usually acellular with mildly elevated protein levels. Patients often spontaneously stabilize neurologically.

One of the authors of this article (Dr. Lieberman) treated a patient who survived for 15 years after being diagnosed with metastatic adenocarcinoma of the colon and then developed a rapidly progressive motor neuron disorder and dementia (unpublished observation). An antibody reactive with anterior horn cells in the spinal cord and pyramidal cells in the cortex was identified in the patient’s serum. Treatment with IV IgG produced a transient improvement in leg strength and ambulation, but the patient died of neurogenic respiratory failure despite a subsequent trial of high-dose methyl prednisolone.

Paraneoplastic Peripheral Neuropathies

Among patients with peripheral neuropathy who were evaluated at a neuromuscular disease center, paraneoplastic peripheral neuropathy was an uncommon diagnosis. In one series of 422 patients evaluated in a neuromuscular disorder referral center, 26 were considered to have possible paraneoplastic neuropathies related to solid tumors.

Subacute Sensorimotor Neuropathy

Subacute sensorimotor neuropathy usually manifests as progressive distal, symmetric sensory loss and weakness, which is more severe in the legs. Lung cancer is the most common associated malignancy. In approximately two-thirds of patients, the neuropathy precedes the diagnosis of cancer or is noted at the same time. The cerebrospinal fluid is usually acellular, and protein concentration may be mildly elevated. Neurophysiologic studies generally indicate an axonal process, and nerve biopsies reveal a mixture of axonal injury and demyelination.

The disorder usually progresses relentlessly, although some patients stabilize after removal of the tumor and some patients appear to benefit from corticosteroid therapy. Women with breast cancer may develop a slowly progressive sensorimotor neuropathy with proximal weakness and upper motor neuron signs. This disorder is frequently indolent.

A novel antigen, CV2, was recently reported as the target antigen in a group of patients presenting with sensorimotor neuropathy, cerebellar degeneration, and uveitis. Optic neuropathy may also occur. The CV2 antigen is a member of the Ulip/CRMP family of proteins, which are involved in axonal growth and guidance. Anti-Hu antibodies were simultaneously present in 20% of patients. Limited pathologic studies suggest that Schwann cells may be the site of injury in the peripheral nervous system, and oligodendrocytes in the CNS.

Acute Polyradiculoneuropathy
Acute polyradiculoneuropathy appears to occur more frequently among patients with Hodgkin’s disease. The clinical features of this disorder in the setting of Hodgkin’s disease are similar to those of idiopathic Guillain-Barré syndrome.[64] Treatment of the Hodgkin’s disease does not clearly modify the course of the neuropathy, and no specific autoantibodies have been identified. Patients may respond to plasmapheresis or IV IgG.[55] Acute polyradiculoneuropathy has also been reported in patients with leukemias, non-Hodgkin’s lymphoma, and multiple myeloma.[62]

Leukemic or lymphomatous infiltration of the peripheral nerves may be clinically indistinguishable from acute polyradiculoneuropathy.[65] Relapsing and remitting forms have also been reported in a variety of solid tumors, leukemia, and lymphoma,[55] but it is possible that these cases are the coincidental idiopathic inflammatory polyneuropathy seen in cancer patients. Several cases of chronic inflammatory demyelinating polyneuropathy have been associated with melanoma.[66,67] Concomitant vitiligo suggests an autoimmune disorder, perhaps directed against shared cell-surface ganglioside antigens.

**Plasma Cell Dyscrasias**

A variety of syndromes are associated with plasma cell dyscrasias.[68] Typical osteolytic multiple myeloma is rarely associated with clinically significant peripheral neuropathy. Most commonly, the neuropathy is a relatively mild sensorimotor neuropathy. Pure sensory neuropathy has also been reported. Patients with osteolytic myeloma develop more severe neuropathies that resemble Guillain-Barré syndrome or chronic inflammatory demyelinating neuropathy.[68] Secondary amyloidosis may also cause an often painful sensorimotor neuropathy in patients. Unfortunately, the progressive neuropathies rarely respond to any form of immunosuppressive therapy.[69]

Although osteosclerotic myeloma represents only 2% of multiple myeloma cases, 50% of patients with osteosclerotic myeloma develop peripheral neuropathy.[68] The association with progressive sensorimotor neuropathy is crucial to recognize, because this neuropathy frequently improves after radiation therapy or chemotherapy. Bone scanning is insensitive, and a metastatic bone survey is necessary to identify the sclerotic bone lesion. M proteins (IgG or IgA) may be missed unless immunoelectrophoresis or immunofixation is performed on both the serum and urine specimen.

Nonmalignant plasma cell dyscrasias may also be associated with neuropathy, and response to treatment varies greatly.[68]

**POEMS Syndrome**

A distinctive syndrome combining polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (known as the POEMS syndrome) is associated with osteosclerotic myeloma. The natural history and features of the neuropathy are the same as those in osteosclerotic myeloma patients without all the diagnostic criteria for POEMS.[68] Chemotherapy may be beneficial in patients with POEMS and disseminated plasmacytoma.

**Mononeuritis Multiplex**

Painful mononeuritis multiplex due to small-vessel vasculitis has been linked to an underlying malignancy in a small number of patients. Among the cancers implicated are SCLC, prostate cancer, endometrial cancer, lymphoma, and renal cell carcinoma.[55] In some patients, the mononeuritis multiplex is part of a more generalized vasculitis, with muscle involvement and elevated sedimentation rate. In other patients, the vasculitis appears to be limited to the peripheral nerves. Nerve biopsy is necessary for diagnosis.

Mononeuritis multiplex may be a presentation of the anti-Hu syndrome. Cases of prostate carcinoma associated with the vasculitic syndrome have been small-cell, undifferentiated carcinomas.[13] In one case, the prostate cancer was associated with anti-Hu antibody. Immunosuppression or plasmapheresis may be beneficial, and removal of a resectable associated cancer has also produced improvement.

Inflammatory brachial neuritis is usually not associated with malignancy, but when paraneoplastic, is
most frequently associated with Hodgkin’s disease.[2] Because metastatic plexopathy is far more common than the paraneoplastic disorder, imaging studies should be performed to identify tumor infiltration of the plexus when paraneoplastic neuritis is considered. Unlike radiation-induced plexopathy, the inflammatory disorder is frequently painful at onset.

**Neuromuscular Junction Disorders**

Typical myasthenia gravis is associated with thymoma in approximately 15% of cases, and autoantibodies against contractile proteins of striated muscle are associated with an increased probability of underlying thymoma.[6] All patients with myasthenia gravis should undergo computed tomography (CT) scanning of the chest to identify thymic neoplasms. In patients with thymoma, the myasthenia gravis may remit after thymectomy.[7] In most cases, the thymoma is not invasive and can be definitively treated by thymectomy.

**Lambert-Eaton Syndrome**

Lambert-Eaton syndrome is one paraneoplastic neurologic disorder for which the immunobiology is clinically relevant, and a molecular understanding of the disease is applicable to the clinic.[70] Approximately 60% of patients with this syndrome have an underlying cancer, usually SCLC.[71] Proximal weakness is a common presenting complaint, but bulbar symptoms are uncommon.

In most patients, Lambert-Eaton syndrome is not a pure motor syndrome; parasthesias are frequently reported. The abnormality of autonomic function has been termed cholinergic dysautonomia[72]; patients may report dry mouth or erectile dysfunction. Characteristic electrophysiologic abnormalities include augmentation of the compound motor action potential with repetitive stimulation.[71]

Antibodies directed against protein epitopes in the voltage-gated calcium channel of presynaptic neurons are present in most patients with Lambert-Eaton syndrome. In animal models, passive transfer of antibody will reproduce the characteristic electrophysiologic abnormality of this syndrome.[70,5] Immunization with synaptotagmin, a component of the P/Q-type calcium channel, will produce autoantibodies and clinical disease in animal models.

Most patients with this disorder benefit from plasmapheresis and immunosuppressive therapy.[71] Drugs that increase the release of presynaptic acetylcholine may also decrease symptoms; 3,4-diaminopyridine is one such agent with relatively minimal side effects.

**Paraneoplastic Syndromes With Muscle Rigidity**

**Stiff-Man Syndrome**

Stiff-man syndrome manifests with muscle stiffness and rigidity that predominates in the paraspinal and abdominal muscles and muscle spasms.[55] Stiff-man syndrome has been reported in association with breast cancer, Hodgkin’s disease, and colon cancer. Paraneoplastic stiff-man syndrome is associated with antibodies against amphiphysin—a synaptic protein involved in vesicle endocytosis. Antibodies against glutamic acid decarboxylase have also been reported, and some patients exhibit antibodies to both amphiphysin and glutamic acid decarboxylase.[55] Patients frequently improve with effective treatment for the underlying tumor, and steroids may also be beneficial.

**Paraneoplastic Neuromyotonia**

Paraneoplastic neuromyotonia is characterized by spontaneous and continuous muscle fiber activity of peripheral origin.[55] Unlike stiff-man syndrome, this abnormal activity persists during sleep, and electromyography shows high-frequency burst discharges.[55] The disorder often develops in association with myasthenia gravis in thymoma. Hodgkin’s disease, plasma cell dyscrasias, and SCLC have been associated with neuromyotonia.[55] Autoantibodies against voltage-gated potassium channels have been found in some patients. The disorder may improve spontaneously or with
plasmapheresis. However, whether antineoplastic treatment benefits these patients in general is unclear.

**Dermatomyositis**

Although most patients with dermatomyositis do not have cancer, they do seem to be at higher risk for the discovery of a cancer.[55] Breast cancer is the most commonly associated cancer in women, and lung and gastrointestinal cancer in men. Tumors of the pancreas, melanoma, germ cell tumors, nasopharyngeal carcinoma, and lymphoma have also been reported.

An immune-mediated intramuscular angiopathy leads to ischemia and muscle fiber necrosis. Deposits of IgG, IgM, and complement are found in the small blood vessels. Cellular inflammatory infiltrates include B cells, macrophages, and CD4+ T cells.

Immunosuppression has not been evaluated specifically in patients with an underlying cancer, but the modalities that are effective in idiopathic dermatomyositis seem effective in the paraneoplastic disorder. It is unclear whether antineoplastic therapy improves the muscle disease in the absence of concomitant immunosuppression.

**Movement Disorders**

If one excludes cerebellar syndromes and POM, paraneoplastic movement disorders are rare. Usually, the movement disorder accompanies other signs of brain-stem dysfunction. Disorders of excess movement predominate. Chorea has been reported in association with brain-stem signs in patients with SCLC,[73-75] in one patient with acute lymphocytic leukemia,[76] and in patients with Hodgkin's disease.[77]

In one patient with SCLC, chorea developed in association with sensorimotor neuropathy, autonomic dysfunction, and bilateral vitreitis and optic neuritis.[78] Antibodies reacting with a novel 76-kd neuronal antigen were present in the serum and cerebrospinal fluid. The patient improved clinically and radiologically after systemic chemotherapy. Antibody immunoreactivity with the optic nerve, retina, or choroid was not demonstrated, so that the relationship of the visual syndrome to the paraneoplastic choreiform disorder is unclear. In another patient with SCLC, rubral tremor in extremity was described as a paraneoplastic syndrome.[79]

Paraneoplastic Parkinsonian syndromes are extremely rare.[80] Rapidly progressive Parkinsonism and autonomic failure have been reported in a man with multiple myeloma. At necropsy, no inflammatory changes were detected in the basal ganglia or elsewhere in the brain.[81] The relationship between the myeloma and the movement disorder is unclear.

**Future Directions**

In the past 5 years, we have seen significant advances in the clinical nosology and our understanding of the immunobiology of paraneoplastic neurologic disorders.[82-84] New onconeural antigens are being identified.

However, clinically and biologically important questions remain. Why does the distribution of neural injury among patients with autoimmune processes directed against apparently identical antigen vary? Why is tissue injury localized to specific regions in disorders marked by widespread distribution of the target antigen throughout the brain? How do antibodies directed against intracellular antigens produce cell injury? What is the role of cellular immunity? Can we manipulate autoimmunity against onconeural antigens to induce tumor regression or suppress tumor invasiveness and metastatic potential, while avoiding neurologic injury?

Elucidation of the mechanisms leading to cell injury in paraneoplastic neurologic disorders has led to the identification of novel onconeural antigens and novel mechanisms of disease. Darnell has
proposed a classification scheme based on the putative biologic functions of the onconeural antigens: neuromuscular junction proteins, vesicle-associated nerve-terminal proteins, neuron-specific RNA-binding proteins, and neuronal signaling molecules.[85]

For disorders in which the target epitopes have been mapped, the relevant immunogenic domains are directly involved in neuronal survival pathways. Darnell has proposed a model of antibody-mediated cell injury in which cellular penetration of antibody—a demonstrated phenomenon for anti-Hu[9]—is followed by antibody-target interaction and deregulation of the gene function required for neuronal survival. Cellular apoptosis may itself provide antigenic molecules for processing by antigen-presenting cells and generation of cell-mediated antineuronal autoimmunity.[86]

Treatment Issues

For most of the paraneoplastic neurologic syndromes, treatment is currently unsatisfactory. When localized cancer is identified, surgical resection may remove an antigenic stimulus, but the neurologic disorder often fails to improve with successful tumor ablation. Immunosuppressive therapy with corticosteroids, plasma exchange, IV IgG, and immunoadsorption, are variably effective.[7] A 75% response rate was seen in a small, heterogeneous series of patients treated with extracorporeal immunoadsorption.[87] For many of the paraneoplastic syndromes, we have no evidence-based rationale for choosing the type or sequence of immunotherapy. The ease and safety of IV IgG led to its frequent choice as first-line therapy for antibody-mediated or antibody-associated disorders.[88]

Consistently effective therapies await a more profound understanding of the mechanisms of disease. We believe that continued application of clinical and molecular expertise will lead to advances in therapy.

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