

Neuromuscular Complications of Cancer Diagnosis and Treatment

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The peripheral nervous system includes the anterior horn cells, dorsal root ganglia, dorsal and ventral roots, plexi, peripheral nerves, neuromuscular junctions, and muscles.¹ Neuromuscular disorders are a common cause of morbidity in the general population, but the problem is magnified in patients with cancer. Neuromuscular dysfunction in cancer patients can be classified as a direct effect of the primary malignancy, a paraneoplastic effect, or a complication of cancer treatment. A variety of other problems, such as steroid myopathy and herpes zoster, also may be encountered.²

Direct Effects of Malignancy

RADICULOPATHIES

Almost any type of cancer can spread to the leptomeninges and cause compression or invasion of nerve roots or cranial nerves.³ Malignancies that may have these effects include breast cancer, lymphoma, lung cancer, gastric cancer, and malignant melanoma.⁴ Neoplastic polyradiculopathies present as radicular pain, sensory loss, weakness, and hyporeflexia and often are associated with signs of meningeal involvement, including neck rigidity and cranial neuropathies.⁵

Such sensory and motor deficits often are widespread and can mimic asymmetric, severe sensorimotor polyneuropathy. Lumbosacral polyradiculopathies commonly present as cauda equina syndrome, with lower back pain radiating to both the lower extremities; these conditions also may result in bladder and/or bowel dysfunction. Focal radicu-

Abstract Neuromuscular disorders are a common cause of morbidity in patients with cancer. They can be a direct effect of the primary malignancy, a paraneoplastic effect, or a treatment complication. Malignant neoplasms may infiltrate or compress nerve roots, plexi, and peripheral nerves, causing various sensory and motor symptoms. Electrodiagnostic testing, cerebrospinal fluid analysis, and neuroimaging are helpful in confirming the diagnosis. Treatment for neuropathies of neoplastic origin involves irradiation and chemotherapy, which may improve pain, but usually does not improve neurologic function. Paraneoplastic syndromes are rare and sometimes result from production of autoantibodies directed against neural antigens present in tumor tissues. They commonly precede any symptoms related to the cancer itself, and discovery of such syndromes necessitates a thorough investigation to look for an occult neoplasm. Treatment of the underlying cancer occasionally improves neurologic function. Both brachial and lumbosacral plexopathies may represent a complication of radiotherapy. Electrodiagnostic tests particularly are helpful; these diagnostics demonstrate the presence of myokymic discharges, which are suggestive of radiation injury. Many chemotherapeutic agents may cause peripheral neurotoxicity and associated acute and chronic peripheral neuropathies, particularly if given to patients with preexisting hereditary or acquired neuropathies. These side effects are a limiting factor in cancer treatment. Other potential neuromuscular problems related to cancer include side effects of steroids and other immunosuppressants, effects secondary to bone marrow transplantation, and infections. Early recognition and management of these disorders will improve patient outcome and quality of life.

lopathies could also result from compression from epidural metastases. In such instances, myelopathy frequently accompanies any focal radiculopathy.

In these cases, a magnetic resonance imaging (MRI) scan with gadolinium usually demonstrates leptomeningeal enhancement or compression of the nerve roots and cranial nerves by the tumor. Cerebrospinal fluid (CSF) analysis almost always reveals an elevated protein level and pleocytosis.⁶ The CSF cytology demonstrates malignant cells in 50% of cases after one spinal tap; the sensitivity increases to 90% after three specimens are obtained and analyzed.^{3,7} Electrodiagnostic testing with nerve conduction studies and electromyog-

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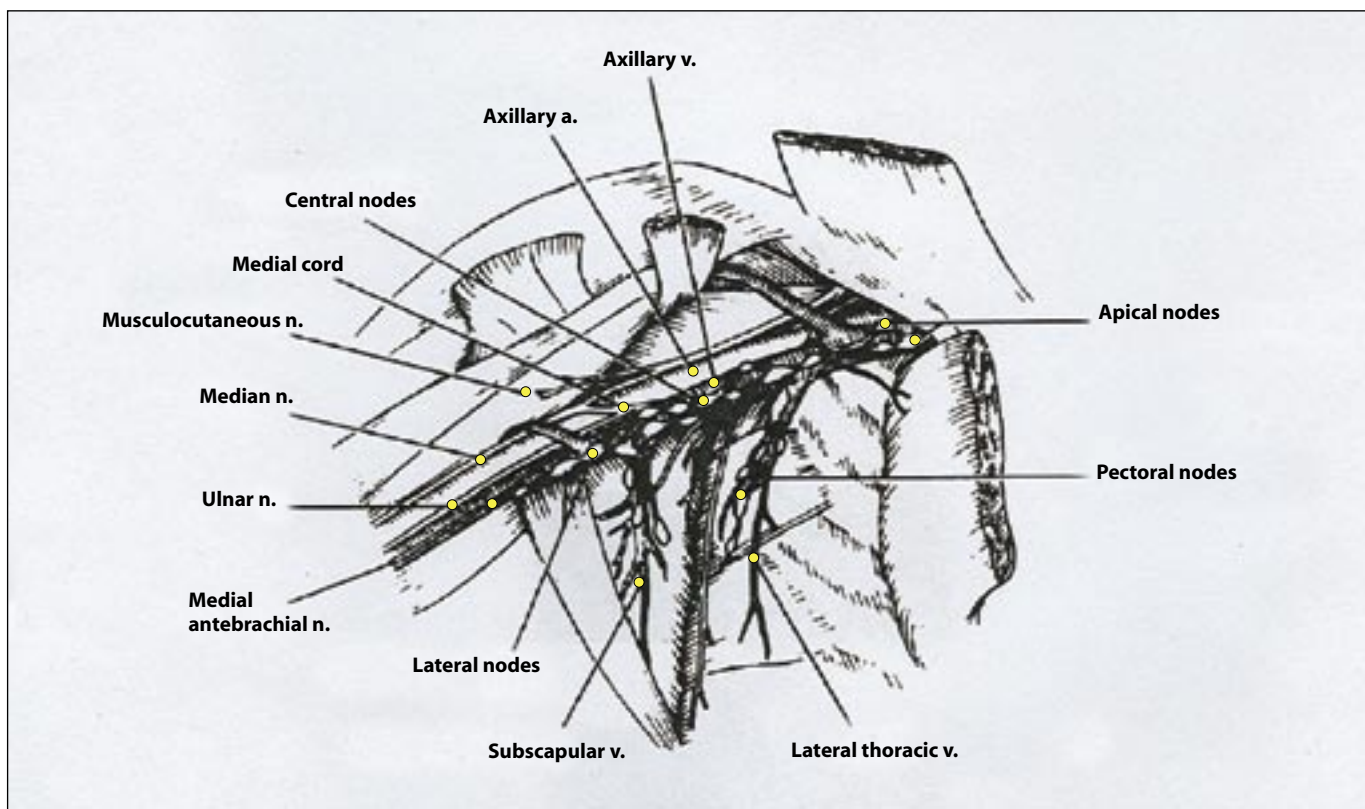


Figure 1 Relation of the Lateral Group of Axillary Lymph Nodes to the Brachial Plexus

Lymphatic spread of lung and breast carcinomas tends to involve the lower trunk (affecting proximal portions of the ulnar and median nerves) and the medial cord of the plexus. Reprinted with permission.¹³

raphy can help to confirm and to characterize nerve root damage and to rule out other conditions that may mimic polyradiculopathy, such as polyneuropathy.⁴

Leptomeningeal carcinomatosis is treated with irradiation or intrathecal chemotherapy. Patients with leukemia, lymphoma, or breast cancer may respond to this treatment relatively well.^{8,9} However, patients diagnosed with other tumors tend to have a poor prognosis and a median survival of 3–6 months.¹⁰ The treatment of spinal epidural metastases involves the use of glucocorticoids (eg, dexamethasone 10 mg IV bolus followed by 4 mg four times daily), local radiation therapy, and surgical decompression in certain cases.

BRACHIAL PLEXOPATHY

Brachial plexopathy in patients with malignancy is most often caused by tumor infiltration or compression. The distinction between neoplastic and radiation plexopathy can be difficult,¹¹ but severe shoulder pain radiating down the medial aspect of the arm, forearm, and fourth and fifth digits is the predominant symptom in the majority of patients with malignant infiltration of the plexus.¹² Neurologic examination discloses weakness, atrophy, and sensory changes in the lower trunk distribution (C8, T1 nerve roots).

Lung and breast carcinomas (and less often lymphoma, sarcoma, and melanoma) are the most common tumors to spread

via lymphatics to the lateral group of axillary lymph nodes, which is in close contact with the lower trunk of the brachial plexus (Figure 1).^{1,6,12,13} Horner's syndrome secondary to involvement of the stellate ganglion and the sympathetic trunk can be seen in more than half of these patients.¹² Involvement of the upper plexus indicates epidural extension of the tumor with involvement of the C5 and C6 roots.¹²

Magnetic resonance imaging may be helpful in imaging a mass in the region of the brachial plexus and is most useful in distinguishing radiation plexopathy from tumor infiltration.¹⁴ In addition, positron emission tomography (PET) scans occasionally are useful in demonstrating early tumors.¹¹

When diagnosis cannot be made by noninvasive means, surgical exploration and biopsy are required.¹⁵ Electrodiagnostic testing better defines and localizes brachial plexopathy, as it rules out other neuropathic causes of sensory disturbance and pain in the upper extremity, such as a cervical radiculopathy or mononeuropathy. Further, the presence of myokymic discharges on needle examination favors radiation plexopathy over neoplastic plexopathy.¹⁶

Radiotherapy is used to treat neoplastic brachial plexopathy, with nearly half of patients showing some relief of pain but no improvement in neurologic function.¹⁷ Chemotherapy can be used as well, especially if the patient already has received radiation to the region. The pain can be disabling, and

although investigators have attempted various procedures to relieve discomfort, including transcutaneous stimulation, paravertebral sympathetic block, and dorsal rhizotomies, these procedures have reported little benefit.¹

LUMBOSACRAL PLEXOPATHY

Lumbosacral plexopathy most commonly is caused by direct extension of intra-abdominal neoplasms. Metastases are less common and account for 25% of cases (Figure 2).¹⁸ Most frequently, colorectal, cervical, testicular, and breast tumors, as well as lymphoma and sarcoma, are involved in this process.

Severe, asymmetric pain in the low back or lower extremities is an early manifestation, followed over a few weeks to months by numbness, paresthesias, weakness, and leg edema. Lower sacral metastases, with or without epidural extension, may cause incontinence, impotence, and perineal pain. Bilateral lumbosacral plexopathies may be noted, usually in those with breast cancer.¹

Both MRI and computed tomography (CT) scans may be useful in demonstrating tumor involvement of the lumbosacral plexus. In particular, the CT scan may aid in detecting bone abnormalities in the sacrum, and MRI may show epidural extension of the tumor;^{2,19} likewise, electrodiagnostic studies are useful to confirm plexopathy and to rule out other neuropathic causes of lower extremity pain, particularly lumbosacral radiculopathy.

As with neoplastic brachial plexopathy, radiation therapy may be used to arrest the progression of deficits and relieve the pain of lumbosacral plexopathy; however, this modality rarely provides neurologic recovery.

PERIPHERAL NEUROPATHY

Peripheral nerve involvement of tumors, although an uncommon phenomenon, results from metastatic compression and invasion. Peripheral neuropathy associated with lymphoma occurs in as many as 10% of patients²⁰ and also has been associated with chronic lymphocytic leukemia.⁷

Lung and breast cancers may involve the mediastinum and may result in lesions of the recurrent laryngeal and phrenic nerves. The sciatic and obturator nerves²¹ most often are involved with pelvic tumors. Single or multiple cranial neuropathies secondary to metastases most commonly affect the third, fifth, sixth, and seventh cranial nerves; these neuropathies sometimes are noted among patients with nasopharyngeal, breast, prostate, and lung cancers. The “numb chin syndrome,” characterized by chin and lower lip numbness in the distribution of the mental branch of the mandibular nerve, particularly suggests the presence of a neoplastic process.^{11,22}

Peripheral neuropathy, a rare complication of multiple myeloma, may be the presenting and predominant feature of the malignancy.²³ It may present as a mild sensorimotor, pure sensory, or subacute remitting and relapsing polyneuropathy.²⁴

Amyloid deposition, a common cause of myeloma and primary systemic amyloidosis neuropathy, may present with prominent dysesthesias and autonomic dysfunction.²³ The

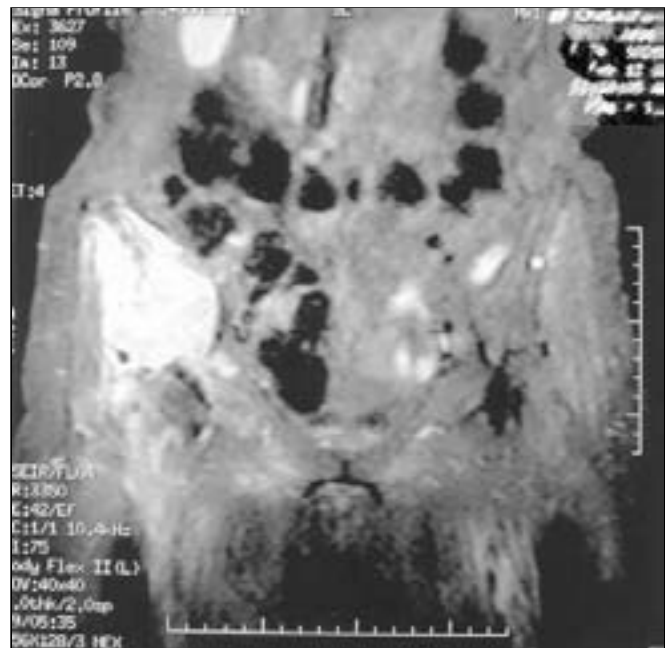


Figure 2 Hyperintensity of the Right Iliac Bone

A 76-year-old woman presented with a 3-month history of right lower extremity pain and weakness. Magnetic resonance imaging of the pelvis revealed hyperintensity of the right iliac bone—a finding consistent with metastatic cancer affecting the lumbosacral plexus.

presence of clinical autonomic dysfunction, such as orthostatic hypotension and constipation alternating with diarrhea, in a patient presenting with a sensorimotor polyneuropathy should raise concern for the presence of amyloidosis. Biopsy of abdominal fat, rectal mucosa, or the sural nerve may provide evidence of amyloid deposition.⁷

Paraneoplastic and Paraproteinemic Neurologic Syndromes

Paraneoplastic syndromes (Table 1) are disorders of an organ or tissue that are associated with cancer but that are not due to the effects of the primary tumor mass; metastatic disease; or nutritional, infectious, metabolic, or treatment-related abnormalities.^{25,26} Instead, they are considered to be “remote effects” of cancer that result in autoimmunity—the sequelae of antibodies or inflammatory cells that are directed against neural antigens expressed by the tumor (eg, onconeural antigens).^{25,27,28}

These syndromes appear before any symptoms related to the cancer itself develop; sometimes, they may precede symptoms by as many as 2 years or more.²⁸ Discovery and treatment of the underlying cancer occasionally lead to improvement in the neurologic symptoms,²⁴ which may respond to immunosuppressive therapy. Table 2 outlines the common features of these syndromes.

SENSORY NEURONOPATHY

This syndrome develops over weeks to months; pain, paresthesias, and sensory loss begin in 60% of patients initially in

Table 1**Paraneoplastic Autoantibodies With Accompanying Syndromes and Most Common Tumors**

AUTOANTIBODY	# OF PATIENTS REPORTED	PARANEOPLASTIC NEUROLOGIC SYNDROME	TUMORS
ANNA-1 (Hu)	> 600	Encephalomyelitis; sensory neuronopathy; chronic gastrointestinal pseudo-obstruction; paraneoplastic cerebellar degeneration; limbic encephalitis	SCLC
VGCC	> 400	Lambert-Eaton myasthenic syndrome; paraneoplastic cerebellar degeneration	SCLC
CRMP-5 (CV-2)	> 200	Encephalomyelitis; chorea; sensory neuronopathy; sensorimotor neuropathy; chronic gastrointestinal pseudo-obstruction; paraneoplastic cerebellar degeneration; limbic encephalitis	SCLC, thymoma
PCA-1 (Yo)	> 200	Paraneoplastic cerebellar degeneration	Ovarian, breast
PCA-2	> 50	Various syndromes	SCLC
ANNA-2 (Ri)	> 50	Brainstem encephalitis	SCLC, breast
Amphiphysin	> 50	Various syndromes, stiff person syndrome	Breast, SCLC
Ma2	> 50	Limbic/diencephalic encephalitis; brainstem encephalitis; paraneoplastic cerebellar degeneration	Testicular, lung
Tr (PCA-Tr)	>20	Paraneoplastic cerebellar degeneration	Hodgkin's lymphoma
ANNA-3	>10	Various syndromes	SCLC

Many paraneoplastic neurologic disorders have coexisting autoantibodies. Myasthenia gravis is not listed but may be associated with thymoma. Modified from Graus et al²⁵ and Pittock et al.²⁶ Abbreviations: SCLC = small cell lung cancer; ANNA-1 = antineuronal nuclear antibody type 1; VGCC = voltage gated calcium channel; CRMP-5 = collapsin response mediated protein 5; PCA-1 = Purkinje cell cytoplasmic antibody, type 1; ANNA-2 = antineuronal nuclear antibody type 2; PCA-2 = Purkinje cell cytoplasmic antibody, type 2; PCA-Tr = Purkinje cell cytoplasmic antibody, type Tr; ANNA-3 = antineuronal nuclear antibody type 3.

the upper extremities and are asymmetric in 40% of cases.²⁹ Patients may complain of subacute loss of fine manual dexterity. Symptoms typically begin before cancer is identified and progress subacutely to involve the limbs, trunk, and face, causing severe sensory ataxia and pseudoathetosis.

This syndrome affects all sensory modalities. Patients typically lose deep-tendon reflexes, but their motor function remains relatively spared. Bladder and bowel disturbances, however, do not occur.¹ Many patients display signs and symptoms of paraneoplastic encephalomyelitis as well,^{6,30,31} less often, autonomic or lower and upper motor neuron involvement is noted, which reflects a more widespread neurologic syndrome.^{32–34}

Paraneoplastic sensory neuronopathy most frequently is associated with the presence of anti-Hu antibodies, which also are known as antineuronal nuclear antibody type 1 (ANNA-1);³⁵ however, other autoantibody markers also have been associated with this phenomenon. In the appropriate patient, a comprehensive paraneoplastic autoantibody panel is recommended for screening.²⁶ The CSF may show mild lymphocytic pleocytosis (20–40 lymphocytes/mm³), a moderate protein elevation, and anti-Hu antibodies. Oligoclonal bands may be present.²⁸ In addition, electrodiagnostic studies typically reveal absence of the sensory responses with relative preservation of motor potentials. Somatosensory-evoked potentials also are absent.⁶ These changes may be asymmetric and commonly are more severe in the upper extremities.

Pathologic changes are seen primarily in the dorsal root ganglia, with neuronal degeneration associated with inflammation and phagocytes.¹ The inflammatory process may advance to include the dorsal column, dorsal root, and peripheral sensory axons.

The malignancy most commonly associated with sensory neuronopathy is small cell lung cancer (SCLC). Other ma-

lignancies encountered less frequently include cancers of the breasts, ovaries, prostate, adrenal gland, as well as neuroblastoma and Hodgkin's lymphoma.^{26,29,31,32} In most patients, the neuronopathy precedes the cancer diagnosis, sometimes by years. Therefore, when an adult develops a relatively pure sensory neuronopathy, particularly when a patient with a smoking history develops one of subacute onset, the practitioner must begin a detailed investigation aimed at detecting an occult neoplasm.¹

The syndrome usually evolves over several months before stabilizing, resulting in significant disability within 6–9 months.²⁴ The differential diagnosis of sensory neuronopathy includes many causes, such as heredity, toxicity (eg, resulting from pyridoxine overdose or abuse, cisplatin, thalidomide [Thalomid], methyl mercury), Sjögren's syndrome, infections (eg, HIV, syphilis), vitamin deficiencies (eg, vitamins B₁₂ and E), primary autoimmune conditions (ie, autoimmune but not associated with cancer), or idiopathic reactions.^{36–38}

In general, treatment has yielded disappointing results. Treating the underlying cancer may prolong survival but does not generally alter the course of the neurologic disease.^{32,39} Similarly, immunosuppressive therapy and plasmapheresis have been attempted with limited success, although there are isolated reports of successful responses of the neuronopathy to immunotherapy.⁴⁰ However, tumors associated with paraneoplastic syndromes may have unusually indolent courses.⁴¹ Aggressive immunosuppression may hasten tumor progression and should be administered with great caution, if at all.^{11,27}

MOTOR NEURON DISEASE

A motor neuron disease syndrome may occur rarely as a paraneoplastic syndrome, although the majority of cases associated with cancer likely are coincidental.⁴² Distinguishing fea-

Table 2**Paraneoplastic Neuromuscular Syndromes**

SYNDROME	CLINICAL FEATURES	TUMORS	ANTIBODIES	EDX (EMG AND AUTONOMIC TESTS)	AFFECTED TISSUE	TREATMENT
Sensory neuropathy	Subacute sensory symptoms and severe sensory loss, sensory ataxia, areflexia, +/- PEM	SCLC Less common: breast, ovarian, prostate, lymphoma	Anti-Hu (ANNA-1) Others: Anti-CV-2 (CRMP-5), ANNA-3	Absent sensory responses (asymmetric, arm > leg), preserved motor potentials	Dorsal root ganglia; may extend to dorsal column and peripheral sensory axons	Treat underlying tumor; immunosuppression and plasmapheresis may hasten tumor growth
Motor neuron disease	Subacute symptoms of LMN, UMN, or both	Lymphoma and thymoma (LMN) Breast (UMN)	Monoclonal gammopathy None	Diffuse denervation changes (LMN)	Anterior horn cells and corticospinal tracts	Treat underlying tumor
Sensorimotor polyneuropathy	Weakness, numbness, areflexia	SCLC, breast Lymphoproliferative disorders	Anti-CV-2 (CRMP-5), ANNA-1 (anti-Hu), PCA-2, amphiphysin, ANNA-2 Monoclonal gammopathy, anti-MAG	Axonal sensorimotor changes Demyelinating neuropathy	Peripheral nerve Peripheral nerve	Treat underlying tumor (irradiation, chemotherapy) Rituximab for WM
Autonomic neuropathy	Orthostatic hypotension, impotence, gastrointestinal dysmotility, impaired sweating, pupillary dysfunction	SCLC, thymoma	Ganglionic acetylcholine receptor, ANNA-1 (anti-Hu), ANNA-2 (Ri), Anti-CV-2 (CRMP-5)	Autonomic dysfunction (QSART, heart rate response to respirations)	Autonomic ganglia	Treat underlying tumor, symptomatic treatment (fludrocortisone, midodrine, sildenafil)
<i>Disorders of continuous motor unit activity</i>						
Stiff-person syndrome	Axial muscle stiffness, spasms	Breast, SCLC, thymoma, lymphoma	Anti-GAD, anti-amphiphysin	Abnormal exteroceptive reflex	Spinal cord inhibitory neurons	IVIg, baclofen, diazepam, plasmapheresis
Isaac's syndrome	Diffuse muscle cramps, stiffness present during sleep	SCLC, thymoma	Voltage-gated potassium channels	Neuromyotonia, myokymia	Peripheral nerve	IVIg, plasmapheresis, phenytoin, carbamazepine
<i>Neuromuscular junction disorders</i>						
Lambert-Eaton myasthenic syndrome	Proximal weakness, fatigability, autonomic dysfunction	SCLC	P/Q subtype voltage-gated calcium channel	Decreased CMAPs with post-exercise facilitation	Presynaptic membrane	3,4-diaminopyridine, pyridostigmine, immunosuppression, IVIg, plasmapheresis
Myasthenia gravis	Oculobulbar and proximal weakness, fatigability, fluctuation of symptoms	Thymoma	Acetylcholine receptors, antistriated muscle	10% decrement in CMAPs after 3 Hz stimulation	Postsynaptic membrane, thymus	Pyridostigmine, immunosuppression, IVIg, plasmapheresis, thymectomy
Inflammatory myopathies	Proximal weakness, skin changes (dermatomyositis)	Ovarian, lung, breast, colorectal		Myopathic changes	Muscle	Corticosteroids, immunosuppressants, IVIg (dermatomyositis)

Abbreviations: PEM = paraneoplastic encephalomyelitis; SCLC = small cell lung cancer; EDX = electrodiagnostic studies; IVIg = intravenous immunoglobulins; CMAPs = compound muscle action potentials; WM = Waldenström's macroglobulinemia; QSART = quantitative sudomotor axonal reflex; MAG = myelin-associated glycoprotein; LMN = lower motor neuron; UMN = upper motor neuron.

tures that may support a true paraneoplastic syndrome include the presence of a specific onconeural antibody (eg, anti-Hu antibody with paraneoplastic encephalomyelitis); resolution or significant improvement of a specific motor neuron syndrome after cancer treatment and without concomitant immunotherapy; cancer presenting within 2 years of diagnosis of motor neuron disease; or unusual symptoms that may include isolated upper or lower motor neuron involvement, associated encephalomyelitis, and rapid onset and evolution.^{25,42,43}

Some patients present with a pure lower motor neuron syn-

drome, known as "subacute motor neuronopathy." This condition classically is associated with lymphoma⁴⁴⁻⁴⁶ and is characterized by progressive, painless, lower motor neuron-type weakness with atrophy, fasciculations, and absent reflexes that affect the legs more than the arms.¹ There is no significant sensory disturbance, and some patients may demonstrate spontaneous improvement.

Laboratory features that may suggest a coexisting lymphoma include the presence of paraproteinemia, raised CSF protein levels, and oligoclonal bands.⁴⁷ A similar association has

been reported with thymoma.⁴⁸ Paraproteinemia, with or without coexisting lymphoma, also has been seen more commonly among amyotrophic lateral sclerosis patients than among the general population; however, treatment of the paraproteinemia has not elicited clinical benefit.⁴⁹

A pure upper motor neuron syndrome resembling primary lateral sclerosis has been described among patients diagnosed with such solid tumors as breast cancer.⁴² This group includes patients who have a lower motor neuron syndrome but who suffer additional involvement of other areas of the nervous system, leading to the diagnosis of paraneoplastic encephalomyelitis.

SENSORIMOTOR POLYNEUROPATHY

Several factors contribute to the development of chronic sensorimotor polyneuropathies in patients with malignancies: weight loss,⁵⁰ chemotherapy, malnutrition, and organ failure.²⁴ The clinical features are not different from those of neuropathies secondary to other causes. Paraneoplastic sensorimotor polyneuropathy is uncommon and is seen most commonly in SCLC and breast cancer. Anti-collapsin response mediated protein-5 (CRMP-5) antibody, also known as anti-CV-2, has been found in some patients with sensorimotor polyneuropathy and SCLC.^{51,52}

Several lymphoproliferative disorders are associated with peripheral neuropathy and the presence of a monoclonal gammopathy. Serum protein electrophoresis is a useful screening test, but diagnostics such as immunoelectrophoresis or immunofixation electrophoresis are more sensitive.⁵³

The most common neuropathies associated with monoclonal gammopathies are the acquired demyelinating polyneuropathies associated with monoclonal gammopathies of undetermined significance (MGUS). These demyelinating neuropathies are known by various names, including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) associated with MGUS (CIDP-MGUS) or distal acquired demyelinating symmetric neuropathy associated with MGUS.

These neuropathies are important to identify for many reasons. First, they do not respond as readily to conventional CIDP treatments. Second, in a significant proportion of patients, MGUS transforms to malignancy such as multiple myeloma or Waldenström's macroglobulinemia.³ In fact, the cumulative probability of a patient with MGUS developing multiple myeloma or a related disorder has been estimated to be about 30% by 15 years and 40% by 25 years.⁵⁴

A rarer disorder associated with sensorimotor polyneuropathy, autonomic neuropathy, and monoclonal protein deposition is primary systemic amyloidosis.⁵⁵ Osteosclerotic myeloma is a rare variant of myeloma that appears in less than 3% of multiple myeloma patients.⁵³ Peripheral nerve involvement, however, is common and occurs in nearly 50% of patients. The polyneuropathy resembles chronic inflammatory demyelinating polyradiculoneuropathy, as it causes slow, progressive, proximal and distal weakness; vibratory and position loss; areflexia, and high CSF protein levels. The results of electrodiagnostic studies reveal an acquired, predominately demyelinating

sensorimotor polyradiculoneuropathy that features very slow conduction velocities, prolonged distal latencies, partial conduction block, and temporal dispersion.

The light-chain monoclonal protein of osteosclerotic myeloma almost always is lambda. Some patients with osteosclerotic myeloma have systemic manifestations that include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, which are referred to collectively as "POEMS syndrome." A bone survey with plain films of axillary and appendicular bones is indicated to look for osteosclerotic myeloma in patients with an acquired demyelinating polyneuropathy, particularly if it is associated with any clinical manifestations suggesting POEMS syndrome, presence of a monoclonal protein (especially of the lambda light-chain type), or a poor response to immunotherapy.

The treatment of the neuropathy includes treating the underlying malignancy with radiation therapy to solitary bone lesions, surgical resection, and the use of chemotherapeutic agents such as prednisone, melphalan (Alkeran), and chlorambucil (Leukeran). Marked improvement of neuropathy has been reported following combined use of surgery, radiation therapy, and chemotherapy.⁵⁶ Treatment with strontium-89 and plasmapheresis also has been effective.⁵⁷ However, although some patients may respond, others continue to progress despite treatment.⁵³

Acquired, demyelinating polyneuropathy occurs in at least 5% of patients with Waldenström's macroglobulinemia. Monoclonal immunoglobulin M deposits on nerve sections have been demonstrated,⁵⁸ and antibodies against myelin-associated glycoprotein are found in up to 50% of cases.⁵⁹ Usually, the neuropathy antedates the hematologic abnormalities by several years. Some patients have been treated successfully with prednisone, chlorambucil, and plasmapheresis.^{58,60} Nucleoside analogues (eg, fludarabine) and the anti-CD20 monoclonal antibody rituximab (Rituxan) are other reasonable choices for the treatment of Waldenström's macroglobulinemia.⁶¹ Rituximab is administered weekly by intravenous (IV) infusion for 4 weeks to start; this course then is repeated 3 months later.⁶²

Mononeuritis multiplex and a symptoms complex reminiscent of acute Guillain-Barré syndrome (GBS) also may occur rarely with paraneoplastic neuropathy in patients with various cancers and Hodgkin's lymphoma.⁶³

AUTONOMIC NEUROPATHY

Involvement of the autonomic nervous system can be seen in various paraneoplastic syndromes.⁶⁴ In general, 10%–30% of patients with paraneoplastic syndrome experience autonomic impairment.^{32,33} Autoimmune autonomic neuropathy, described among patients with SCLC, thymoma, and other malignancies, occasionally may be paraneoplastic, although it more typically is primary autoimmune and follows a viral infection. Some of these paraneoplastic, autoimmune, and autonomic neuropathies are associated with autoantibodies to ganglionic acetylcholine receptors.⁶⁵

The presenting symptoms of autoimmune paraneoplastic

disorders may include orthostatic hypotension, impotence, upper and lower gastrointestinal dysmotility, impaired sweating, urinary retention, and pupillary dysfunction.³ Chronic intestinal pseudo-obstruction is a rare syndrome that has been associated with SCLC.^{65,66}

Paraneoplastic dysautonomia may improve as the tumor is treated and other drugs are used, such as midodrine (Pro-Amatine), fludrocortisone, and pyridostigmine for orthostatic hypotension and cholinergic drugs for bladder and bowel dysfunction. Nonpharmacologic measures, including adequate salt and fluid intake, use of compression stockings, and a 4-inch elevation of the head of the bed, are of particular help in treating orthostatic hypotension.

DISORDERS OF CONTINUOUS MUSCLE FIBER ACTIVITY

Stiff-person syndrome, also known as stiff-man syndrome, and Isaac's syndrome are two disorders of excessive, involuntary motor activity that occasionally have been encountered in cancer patients.⁶⁷

Stiff-person syndrome is characterized by progressive muscle stiffness and spasms affecting predominantly the axial muscles. Its painful spasms are triggered by sudden noise or movement,²⁴ and stiffness disappears during sleep. Antibodies against glutamic acid decarboxylase 65 are found in > 90% of non-paraneoplastic patients;⁶⁸ this finding may lead to decreased gamma-aminobutyric acid (GABA)-mediated spinal and supraspinal inhibition.⁶⁹

Anti-amphiphysin antibodies sometimes are associated with stiff-person syndrome, especially in women with the syndrome who have breast cancer.^{26,70} Lymphoma, SCLC, and thymoma⁷ also have been reported less commonly among individuals with this syndrome. "Atypical" stiff-person syndrome includes distal limb rigidity, or stiff-limb syndrome, and progressive encephalomyelitis with rigidity; pathologic findings may include encephalomyelitis with prominent grey matter involvement. Generally, both treatment response and prognosis are poor when compared with those of patients with classic stiff-person syndrome.⁷¹

Stiff-person syndrome typically is not associated with a cancer diagnosis.⁷² Patients with the syndrome may respond to high benzodiazepine doses, IV immunoglobulins, plasmapheresis, or immunosuppression.^{73,74}

Isaac's syndrome, or acquired neuromyotonia, presents with diffuse muscle stiffness at rest, muscle cramps, and spasms, with muscle activity persisting during sleep. Antibodies against voltage-gated potassium channels are associated with the syndrome.⁷⁵ Results from electrodiagnostic studies disclose neuromyotonia and/or myokymia; myokymic discharges are recurring bursts of single motor unit action potentials that fire at a frequency of 5–150 Hz and occur at regular or irregular intervals; neuromyotonic discharges have somewhat similar characteristics, but the bursts are more prolonged and persistent, begin and end abruptly, fire at a frequency of 150–300 Hz, and have a waning amplitude.⁷⁶

Malignancies associated with these symptoms include SCLC and thymoma.⁷⁷ Phenytoin and carbamazepine may

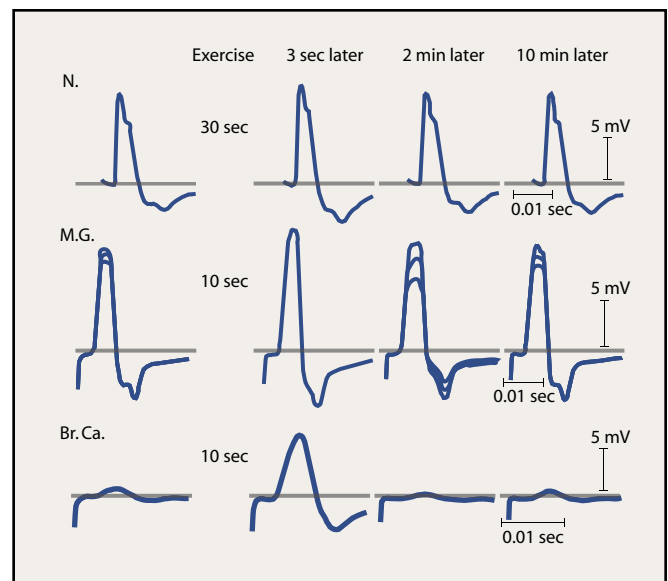


Figure 3 Effect of Exercise on the Action Potential of the Hypothenar Muscles

The response of the rested muscle (far left) is compared with the responses 3 seconds, 2 minutes, and 10 minutes after the end of a maximal voluntary muscle contraction. Each record represents three superimposed action potentials obtained at a rate of 3 Hz. **N.** = Normal responses. **M.G.** = Responses of a patient with generalized myasthenia gravis, with progressive decline in amplitudes during 3 Hz stimulation. Three seconds after exercise, the defect is repaired, and there is an increase in amplitudes. Two minutes after exercise, the defect is more marked than it was initially. At 10 minutes, the amplitudes return to baseline. **Br. Ca.** = Patient with bronchogenic carcinoma and Lambert-Eaton myasthenic syndrome. The initial response is very small but increases markedly (facilitates) 3 seconds after brief exercise. It returns to baseline at 2 minutes post exercise. Reprinted with permission.¹³

help the muscle spasms;⁶ plasmapheresis and IV immunoglobulins have benefited some patients.⁷

PARANEOPLASTIC SYNDROMES OF THE NEUROMUSCULAR JUNCTION

Such autoimmune syndromes are characterized by production of antibodies against various components of the neuromuscular junction. Lambert-Eaton myasthenic syndrome (LEMS) is a presynaptic disorder secondary to the production of antibodies against the P/Q subtype of voltage-gated calcium channels; this results in decreased release of acetylcholine and neuromuscular junction failure.⁷⁸ These antibodies are found in the majority of patients.⁷⁹

Clinical features of these syndromes include progressive proximal weakness, fatigability, reduced or absent deep-tendon reflexes, and dysautonomic symptoms (eg, dry mouth, impotence). Oculobulbar manifestations are not uncommon but are relatively mild.⁸⁰

The results of electrodiagnostic testing reveal very small compound muscle action potentials (CMAPs) that increase after brief exercise or high rates of repetitive stimulation (Figure 3).¹³ Slow repetitive nerve stimulation reveals a fall in CMAP amplitude and area.

About one-half to two-thirds of patients with LEMS have an associated malignancy—and the neoplastic condition usually is SCLC.^{1,81} Other autoimmune syndromes (eg, autoimmune thyroid disease, pernicious anemia, and rheumatoid arthritis) can occur with LEMS.

The diagnosis of LEMS often is delayed.⁸⁰ Diagnosis should lead to a thorough investigation for an underlying malignancy, since early detection and antineoplastic treatment are the most important therapeutic modalities.²⁷ Either CT or MRI scans of the chest should be performed; if the results of these studies are normal, the tests should be repeated regularly, as indicated. In addition, a PET scan may be used to detect early tumors.¹¹

Pyridostigmine, in the same doses used to treat myasthenia gravis (MG), might improve mild symptoms. Administration of 3, 4-diaminopyridine (3, 4-DAP) facilitates acetylcholine release and increases neuromuscular junction transmission, producing significant improvement in most patients. The drug is started at 20 mg/day and the dose is increased gradually to a maximum of 60–80 mg/day divided into three doses, since seizures can result from use of higher doses. The drug has not been approved for clinical general use, but it may be obtained on a compassionate-use basis for the individual LEMS patient.^{82,83} However, immunosuppressive therapy, IV immunoglobulins, and plasmapheresis have a transient effect only on patients with LEMS.

Myasthenia gravis is associated with thymoma in 10% of cases, whereas 30% of patients who present with thymoma have MG.¹ These patients commonly suffer oculobulbar and respiratory muscular effects, and a variable degree of proximal arm and leg weakness is found. Patients get weaker with exercise and improve with rest; on electrodiagnostic studies, the CMAPs usually are normal at rest but begin to drop with low frequency repetitive stimulation (Figure 3).¹³ The majority of patients have antibodies against acetylcholine receptors; however, elevated antistriatal muscle antibody levels are found in 90% of patients with MG that is linked to thymoma. The presence of antistriatal muscle antibodies (eg, anti-titin antibodies)⁸⁴ in MG patients diagnosed when under 60 years of age indicates associated thymoma, whereas detection of these antibodies is much less predictive among patients with later-onset MG.

Thymoma with MG most commonly occurs in older patients, and all MG patients should undergo chest CT at the time of diagnosis. In patients who present initially with thymoma, a careful evaluation for MG is indicated, since subclinical MG increases surgical morbidity. Because of the tumor propensity for local invasion, thymectomy is indicated for all patients diagnosed with thymoma. Following thymectomy, patients can be monitored for recurrence by chest re-imaging and by following antistriatal antibody levels (eg, anti-titin antibodies).⁸⁴ Treatment of MG in cancer patients is similar to that for patients without tumors.

INFLAMMATORY MYOPATHIES

Both dermatomyositis and polymyositis have been associated with malignancy,⁸⁵ although the risk is substantially greater for dermatomyositis. It has been estimated that the risk of can-

cer in patients with dermatomyositis is four fold higher than it is among the general population during the 4 years both before and after diagnosis. For polymyositis, the risk is much less during the 1–5 years following diagnosis.⁸⁶

The most frequent tumors associated with inflammatory myopathies are those affecting the ovaries, lungs, breasts, stomach, colon, and rectum and non-Hodgkin's lymphoma.⁸⁷ Cancer and dermatomyositis usually tend to appear within 2 years of each other. Malignancy in dermatomyositis is more common among older patients, although it also has been reported in young adults.⁸⁵ The clinical and laboratory findings in patients with cancer-associated inflammatory myopathies are similar to those seen among patients with idiopathic disease. Proximal muscle weakness, elevated serum creatine kinase levels, electrodiagnostic evidence of myopathy, and inflammatory changes on muscle biopsy are common findings.

The evaluation for cancer should include a careful history and physical examination (including rectal, pelvic, testicular, and breast examinations), screening laboratory tests (eg, blood count, serum chemistries), chest x-ray, and stool occult blood screening. Women should have a mammography and pelvic ultrasonography or CT. Patients with dermatomyositis, but perhaps not those with polymyositis, should undergo continued surveillance.⁸⁸

Corticosteroids and other immunosuppressants can be used, although paraneoplastic dermatomyositis may be less responsive to steroids.⁶ Treatment of the tumor has inconsistent effects on the course of muscle disease.

A rare, acute, rapidly progressive, necrotizing myopathy has been reported among patients with SCLC and breast, gastrointestinal, and bladder cancers.⁶ Other causes of muscle disease in cancer patients include disuse atrophy and toxic and metabolic myopathies.

Iatrogenic Effects

RADIATION-INDUCED PLEXOPATHY

Radiation therapy affects the nervous system in different ways, including direct damage to neural structures in the radiation port resulting from vascular endothelial injury and fibrinoid necrosis with resultant perivascular fibrosis and nerve damage. It also can cause new tumors that may compress or destroy neurologic structures.

BRACHIAL PLEXOPATHY

Typically, radiation-induced plexopathy occurs 1 year or more (range, 4 months to 26 years; mean, 6 years) after radiation therapy with doses of 6,000 cGy or greater.¹ Other risk factors for the development of brachial plexus injury are concomitant use of chemotherapy and young age.⁸⁹ Patients typically present with *painless* sensory disturbance and weakness of the arm and hand with sensory symptoms, often progressing to involve the entire upper extremity. Lymphedema is seen in 45% of patients.¹²

The upper trunk, and, less commonly, the entire plexus, is affected in the most patients; isolated lower trunk involvement (especially with severe pain and Horner's syndrome) is strongly

Table 3
Chemotherapeutic Agents Associated With Neuropathies

DRUG	CLINICAL FEATURES	ELECTROPHYSIOLOGIC CHANGES
Vinca alkaloids (eg, vincristine)	Symmetric sensorimotor polyneuropathy; autonomic neuropathy, rarely cranial neuropathies	Axonal sensorimotor polyneuropathy; denervation in distal muscles
Cisplatin	Predominant sensory neuronopathy; sensory ataxia; Lhermitte's sign	Low-amplitude or unobtainable SNAPs; motor NCS and EMG usually normal
Taxanes (eg, paclitaxel)	Symmetric predominantly sensory polyneuropathy; rare autonomic symptoms	Axonal sensorimotor polyneuropathy; denervation in distal muscles
Suramin:		
• Axonal neuropathy	Symmetric predominantly sensory polyneuropathy	Axonal sensorimotor polyneuropathy
• Demyelinating neuropathy	Subacute sensorimotor neuropathy with diffuse proximal>distal weakness; areflexia; increased CSF protein	Acquired, sensorimotor demyelinating neuropathy; EMG with decreased recruitment and denervation changes
Thalidomide	Symmetric sensorimotor polyneuropathy; autonomic neuropathy; sensory ataxia and spasticity in severe cases	Axonal sensorimotor polyneuropathy; denervation in distal muscles
Oxaliplatin	Predominant sensory neuronopathy; sensory ataxia; Lhermitte's sign	Low-amplitude or unobtainable SNAPs; EMG with neuromyotonic discharges in acute cases

Modified from Amato et al.³ Abbreviations: SNAPs = sensory nerve action potentials; NCS = nerve conduction study; EMG = electromyography; CSF = cerebrospinal fluid.

suggestive of metastatic plexopathy.¹² The relative resistance of the lower trunk of brachial plexus to the effects of radiation is related to the protective effect of the clavicle and the short distance the trunk travels through the radiation port.¹³

Electrodiagnostic testing can be useful in differentiating between cancer- and radiation-induced plexopathy. The diagnostic measure indicates the presence of myokymic discharges,⁷⁶ which are seen commonly with radiation plexopathy but only rarely with neoplastic plexopathy.⁶

LUMBOSACRAL PLEXOPATHY

Radiation-induced lumbosacral plexopathy (also known as radiculoplexopathy, because nerve roots are frequently involved as well) presents with painless unilateral or asymmetric bilateral lower extremity weakness. Distal muscles in the L5–S1 distribution predominantly are affected, and physical examination reveals evidence of sensory loss and areflexia.

The onset of symptoms following radiation therapy varies and ranges between 1–31 years, with a mean of 5 years.³ The disease gradually progresses, resulting in significant, severe disability. The absence of tumor on pelvic CT or MRI and evidence of myokymic discharges on electrodiagnostic testing are other supportive features for radiation-induced plexopathy.

Although there is no effective treatment for radiation-induced plexopathy, a combination of pentoxifylline (800 mg/day) and vitamin E (1,000 IU/day) administered orally for 6 months has been effective in reversing chronic radiotherapy damage in a small number of patients.⁹⁰

Another delayed effect of radiation therapy is the development of malignant peripheral nerve sheath tumors in the irradiated site after years of treatment.⁹¹

CHEMOTHERAPY

The development of peripheral neuropathy is a common factor in limiting therapy with chemotherapeutic agents (Ta-

ble 3).^{3,92} Symptoms may appear during or shortly after drug administration; for some drugs, the effect is more delayed, appearing only after chemotherapy ends. Patients with a known history of diabetic, alcoholic, or hereditary neuropathies are more prone to develop acute deterioration following administration of chemotherapeutic agents.⁹³

VINCRIStINE

Vinca alkaloids (vincristine, vinblastine, vindesine) bind to intracellular tubulin,⁹² disrupt cell division, and interfere with axonal transport. Vincristine is the most toxic of this group.

The severity of peripheral neuropathy caused by this drug is a function of both dose and duration of therapy. It causes mixed sensorimotor polyneuropathy with paresthesias in the feet and finger tips and early loss of ankle jerks; muscle cramps and weakness follow in severe disease. Autonomic dysfunction may occur, along with orthostatic hypotension, constipation, and impotence.⁶⁴ A rapidly progressive syndrome of severe polyneuropathy resembling acute GBS may develop when vincristine is given to patients with hereditary neuropathies (eg, Charcot-Marie-Tooth disease), even when administered at standard doses.^{93,94} For this reason, a careful history (especially family history) and physical examination should be performed prior to administration of vincristine to detect underlying hereditary neuropathy.

Recovery begins soon after the drug is stopped, although it usually takes months or years and may be incomplete. Gastrointestinal motility typically recovers relatively quickly.

CISPLATIN

Cisplatin neurotoxicity is dose-dependent and follows cumulative doses of 400 mg/m² or more; however, neuropathy may follow exposure to amounts as low as 200 mg/m².⁹² Characteristically, cisplatin-associated neuropathy is purely sensory in nature and is related to the sensory ganglionopathic effects

of the drug on the dorsal root ganglia. Paresthesias, numbness, and tingling sensations are followed by loss of deep-tendon reflexes, vibration, sensory ataxia, and gait instability. Strength, however, is usually unaffected. In addition, patients may develop Lhermitte's sign (an electric sensation between the shoulder blades and down the spine) secondary to posterior column demyelination.

Results of electrodiagnostic studies show absent or reduced sensory responses with preservation of motor nerves and normal needle electrode examination. A characteristic phenomenon of cisplatin neuropathy is "coasting," or onset and progression of symptoms after completion of cisplatin treatment.⁶ Occasionally, this phenomenon is seen with vincristine and other toxic polyneuropathies.⁹⁵

Recovery is slow, occurring over months to years, and often is incomplete. Various agents have been used to ameliorate or prevent cisplatin neuropathy, including amifostine (Ethyol) and glutathione, with promising results.⁹²

TAXANES

Both paclitaxel and docetaxel (Taxotere) can produce symmetric, predominantly sensory polyneuropathy, which may begin within 1–3 days after a single high-dose treatment. Autonomic symptoms occur rarely.⁶⁴ The neuropathy usually improves when the drug is discontinued.

SURAMIN

Suramin-induced neuropathy produces a combination of sensory and motor symptoms. A subacute syndrome of sensorimotor polyneuropathy with diffuse weakness that resembles GBS also can be seen, with patients experiencing areflexia and flaccid paralysis. Suramin neuropathy may be prevented by carefully monitoring plasma levels and maintaining a peak level less than 350 $\mu\text{g/mL}$.⁹²

THALIDOMIDE

Thalidomide (Thalomid), an angiogenesis inhibitor, has been effective in patients with refractory or relapsed multiple myeloma. Peripheral neuropathy has been seen in more than two-thirds of patients treated for 6 months or more with this drug.

Motor, sensory, and autonomic dysfunction is common with thalidomide therapy. In severe cases, the pyramidal tracts and posterior columns may become involved, causing profound sensory ataxia and spasticity. Symptoms may improve after discontinuation of the drug.⁹⁶

OXALIPLATIN

Neuropathy following oxaliplatin (Eloxatin) administration is very common; this predominantly sensory phenomenon occurs in two forms. The acute form of this neuropathy is seen in the majority of patients; frequently, it is noted during or shortly after the infusion and is self-limited. Patients develop dyesthesias exacerbated by cold and sometimes muscle contractions and weakness.

Chronic oxaliplatin-induced neuropathy is dose-related, occurs after prolonged treatment, and resembles cisplatin neuropathy. Results of electrodiagnostic studies done during acute symptoms phase display neuromyotonic discharges, whereas a predominantly sensory neuronopathy with low or absent sensory nerve action potentials is seen in chronic cases.⁹⁷ Preventive measures that can be used include IV administration of calcium and magnesium solutions before and after oxaliplatin administration.⁹⁸

OTHER AGENTS

Other chemotherapeutic agents that may be associated with peripheral neuropathy include cytarabine, procarbazine (Matulane), etoposide, and ifosfamide (Ifex).⁶

Other Neuromuscular Complications

Although cancer patients must face problems related to paraneoplastic disorders, treatment-related neuromuscular toxicities, and neoplasms themselves, they also may encounter various other problems, including steroid myopathy, neuropathy from immunosuppressive agents used following bone marrow transplantation (eg, tacrolimus [Prograf], cyclosporine), and herpes zoster infection.³

Autoimmune neuromuscular complications (myositis, MG, GBS, and CIDP) also have been reported with bone marrow transplantation and the development of graft-versus-host disease.⁷

Summary

Neuromuscular complications occur frequently in patients with cancer and are a source of considerable morbidity. Direct effects related to leptomeningeal infiltration, peripheral neuropathies that are often multifactorial in origin, various paraneoplastic syndromes, and/or treatment-related complications are seen commonly in oncologic practices. Hopefully, early recognition and management of these disorders will improve patient outcome and quality of life.

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