Plenary
Neuromuscular Complications of Cancer and its Treatment

Photo by Michael D. Stubblefield, MD
Plenary: Neuromuscular Complications of Cancer and Its Treatment

Steven Vernino, MD, PhD
Kurt A. Jaeckle, MD
Eric Lis, MD
Gary J. Bennett, PhD
Andrea L. Cheville, MD, MSCE
Michael D. Stubblefield, MD
Please be aware that some of the medical devices or pharmaceuticals discussed in this handout may not be cleared by the FDA or cleared by the FDA for the specific use described by the authors and are “off-label” (i.e., a use not described on the product’s label). “Off-label” devices or pharmaceuticals may be used if, in the judgment of the treating physician, such use is medically indicated to treat a patient’s condition. Information regarding the FDA clearance status of a particular device or pharmaceutical may be obtained by reading the product’s package labeling, by contacting a sales representative or legal counsel of the manufacturer of the device or pharmaceutical, or by contacting the FDA at 1-800-638-2041.
Plenary: Neuromuscular Complications of Cancer and Its Treatment

Table of Contents

Course Objectives & Course Committee 4
Faculty 5
Paraneoplastic Neuromuscular Disorders 7
   Steven Vernino, MD, PhD
Plexopathy and Radiculopathy in Cancer 13
   Kurt A. Jaeckle, MD
Update on Imaging of the Spine and Plexus in Cancer 19
   Eric Lis, MD
Mechanisms of Neurotoxicity in Cancer 27
   Gary J. Bennett, PhD
Neuropathic Pain in Cancer 33
   Andrea L. Cheville, MD, MSCE
Neuromuscular Complications of Radiation Therapy 37
   Michael D. Stubblefield, MD
CME Questions 43

Dr. Vernino is a technical consultant for Athena Diagnostics. Any conflict of interest was resolved according to ACCME standards. All other authors/faculty have nothing to disclose.

Course Chair: Michael D. Stubblefield, MD

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
Objectives

Objectives - This course provides a comprehensive overview of spasticity evaluation and management. Participants will acquire skills to (1) explain the controversies in evaluation, surgical management and new treatment options in neurogenic thoracic outlet syndrome, (2) discuss whether the use of electrodiagnostic studies in tarsal tunnel syndrome is under or over utilized, and (3) describe the pros and cons in the role of electrodiagnostic studies in the evaluation and management of piriformis syndrome.

Target Audience:
- Neurologists, physical medicine and rehabilitation and other physicians interested in neuromuscular and electrodiagnostic medicine
- Health care professionals involved in the management of patients with neuromuscular diseases
- Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research

Accreditation Statement - The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

CME Credit - The AANEM designates this live activity for a maximum of 5.5 AMA PRA Category 1 Credits™. If purchased, the AANEM designates this enduring material for a maximum of 6.25 AMA PRA Category 1 Credits™. This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Physicians should claim only the credit commensurate with the extent of their participation in the activity. CME for this course is available 09/2011 - 09/2014.

CEUs Credit - The AANEM has designated this live activity for a maximum of 3.25 AANEM CEUs. If purchased, the AANEM designates this enduring material for a maximum of 6.25 CEUs.
Plenary: Neuromuscular Complications of Cancer and Its Treatment

Faculty

Gary J. Bennett, PhD
Professor and Canada Senior Research Chair
Department of Anesthesiology
Faculty of Dentistry
The Alan Edwards Center for Research on Pain
McGill University
Montreal, Quebec, Canada

Dr. Bennett is professor and Canada Senior Research Chair in the Department of Anesthesia, the Faculty of Dentistry, and the Alan Edwards Centre for Research on Pain at McGill University, in Montreal, Canada, and adjunct professor in the Department of Anesthesiology, School of Medicine, University of California, San Diego. He earned his bachelor’s degree in psychology in 1970 from Rutgers University and his doctorate in experimental psychology from the Medical College of Virginia, Virginia Commonwealth University in 1978. In the same year, he joined the Neurobiology and Anesthesiology Branch (NAB) of the National Institute of Dental Research, National Institutes of Health in Bethesda, Maryland, as a public health service postdoctoral fellow. He was appointed to the permanent staff of NAB in 1979, and he was made chief of the Neuropathic Pain and Pain Measurement Section in 1991. In 1996, he became professor in the Department of Neurology at Medical College of Pennsylvania, Hahnemann University in Philadelphia. He joined McGill University in 2001. He has served on the American Pain Society’s Board of Directors and on the Editorial Board for Pain (1986-1999), the journal of the International Association for the Study of Pain, and currently serves on the Editorial Board for Pain Medicine, the journal of the American Academy of Pain Medicine. He has served on the Board of Directors of the Reflex Sympathetic Dystrophy Syndrome Association of America, where he was Director of Research, and received their Scientific Achievement Award in 2000. He was awarded the American Pain Society’s Frederick W.L. Kerr Basic Science Research Award in 1996, and the American Academy of Pain Medicine’s Founder’s Award in 2001. For the past 30 years, his research has focused on peripheral nerve disorders and the mechanisms underlying neuropathic pain syndromes.

Kurt A. Jaeckle, MD
Professor of Neurology and Oncology
Department of Neurology and Oncology
Mayo Clinic Florida
Jacksonville, Florida

Dr. Kurt A. Jaeckle is a consultant in neurology and oncology and a professor of neurology and professor of oncology at the Mayo Clinic Florida in Jacksonville and is Board Certified in neurology. Dr. Jaeckle has served as a principle and co-investigator on several national and international Phase I-III clinical therapeutic trials, evaluating new chemotherapeutic and novel molecular targeted agents for treatment of patients with brain tumors. He has numerous publications in the field, including investigations regarding neoplastic and treatment-related plexopathy, polyradiculopathy, and paraneoplastic diseases. He is currently co-chair of the Neurooncology Committee for the National Cancer Institute’s (NCI) Cooperative Group ACTION (formerly with the North Central Cancer Treatment Group) and a member of the NCI Brain Malignancies Steering Committee. He has administratively served on several boards and committees for the American Academy of Neurology, the Society of Neurooncology, and the United Council for Neurologic Subspecialties.

Andrea L. Cheville, MD, MSCE
Associate Professor
Department of Physical Medicine and Rehabilitation
Mayo Clinic
Rochester, Minnesota

Dr. Cheville’s investigative and clinical interests encompass cancer rehabilitation, pain, and functional outcome measurement. She joined the Mayo Clinic’s Department of Physical Medicine and Rehabilitation in 2006. Prior to this, she received a bachelors of arts degree from Swarthmore College, a medical degree from Harvard Medical School, and masters of clinical epidemiology from the University of Pennsylvania. During Dr. Cheville’s rehabilitation residency at the Kessler Institutes in New Jersey, she became interested in the relationship between pain and function in chronic disease states. During a 2-year pain and palliative care fellowship at Memorial Sloan-Kettering Cancer Center, she pursued this interest and was subsequently recruited by the
University of Pennsylvania Health System to develop a Cancer Rehabilitation Program. Dr. Cheville succeeded in creating a dynamic and nationally-recognized program and served as its director for 7 years before moving to the Mayo Clinic. Dr. Cheville has subspecialty board certifications in pain medicine and in palliative and hospice medicine. In addition to her clinical responsibilities as a palliative care consultant, Dr. Cheville devotes her time to researching functional morbidity related to cancer, its treatment, and related symptoms. Epidemiological and statistical modeling approaches are central to Dr. Cheville’s work which has an overarching goal of developing more patient-centric, economical, and effective models of supportive care delivery.

Eric Lis, MD
Associate Clinical Attending
Director of Neurointerventional Radiology
Memorial Sloan-Kettering Cancer Center

Assistant Professor of Radiology, Weill Cornell Medical School
New York, New York

Dr. Lis is board certified in diagnostic radiology with an added certificate of qualification in neuroradiology. As the director of the neurointerventional service at Memorial Sloan-Kettering Cancer Center, his primary clinical expertise is in the imaging and neurointervention of the spine and proximal peripheral nervous system in patients with cancer. He has authored many articles and chapters on the diagnosis and imaging of spine abnormalities with special interests toward patients with cancer. Dr. Lis is an active member of the American Society of Spine Radiology and the American Society of Neuroradiology.

Michael D. Stubblefield, MD
Associate Attending Physiatrist
Chief, Rehabilitation Medicine Service
Department of Neurology, Rehabilitation Medicine Service
Memorial Sloan-Kettering Cancer Center

Assistant Professor of Rehabilitation Medicine
Department of Physical Medicine and Rehabilitation
Weill Medical College of Cornell University
New York, New York

Dr. Stubblefield is board certified in physical medicine and rehabilitation, internal medicine, and electrodiagnostic medicine. His primary clinical expertise is in the identification, evaluation, and treatment of neuromuscular, musculoskeletal, and functional complications of cancer and its therapy, particularly those caused by radiation and chemotherapy. Dr. Stubblefield has authored numerous articles and book chapters on cancer rehabilitation and is the senior editor of Cancer Rehabilitation: Principles and Practice, the only comprehensive textbook on cancer rehabilitation. Dr. Stubblefield serves on the Board of Directors of the American Association of Neuromuscular and Electrodiagnostic Medicine and is the chair-elect of the Medical Council of the American Association of Physical Medicine and Rehabilitation.

Steven Vernino, MD, PhD
Professor
Department of Neurology
University of Texas Southwestern Medical Center
Dallas, Texas

Dr. Vernino is professor of neurology and neurotherapeutics at University of Texas Southwestern Medical Center in Dallas where he also serves as program director for the Neurology Residency Program, vice-chair for Academic Affairs, and director of the Clinical Autonomic Disorders Laboratory. He received his medical degree from Baylor College of Medicine in Houston, where he also earned a doctorate in neuroscience. He then completed a residency in neurology and a fellowship in electromyography and neuroimmunology at the Mayo Clinic in Rochester, Minnesota. Dr. Vernino is board certified in neurology and electrodiagnostic medicine. He is a member of the American Neurological Association and a fellow of the American Academy of Neurology. He also serves on the Clinical and Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Dr. Vernino’s research interests include the evaluation and treatment of autoimmune and paraneoplastic neurologic disorders and studies of neurological autoantibodies. He has been principal investigator or coinvestigator on several National Institutes of Health (NIH)-funded clinical trials and NIH-funded basic research projects. He was awarded the 1998 Founders Award from the American Academy of Neurology for his work on antibody-mediated autonomic neuropathy. Dr. Vernino has authored or coauthored more than 125 research articles, book chapters, invited reviews, and abstracts, which have been published in such journals as the New England Journal of Medicine, Neurology, Journal of Neuroscience, and Journal of Clinical Investigation.
INTRODUCTION

Paraneoplastic neurological disorders (PNDs) are a group of heterogeneous neurological disorders that occur in patients with cancer. These result from remote immunological effects of malignancy rather than from metastases or direct invasion of the nervous system by the tumor. PNDs typically present before the diagnosis of cancer. Hence, early clinical suspicion is of paramount importance. Overall, PNDs are rare and estimated to affect only 0.01% of cancer patients. However, there are some notable exceptions. Myasthenia gravis (MG) is seen in as many as 15% of patients with thymoma. Up to 3% of patients with small cell lung carcinoma (SCLC) have some form of PND, most notably Lambert-Eaton myasthenic syndrome (LEMS). Among patients with osteosclerotic plasmacytoma, up to half have a paraneoplastic peripheral neuropathy. Although a variety of tumors have been reported in association with PNDs, SCLC, adenocarcinoma of breast and ovary, and thymoma are the ones most commonly encountered in practice.

The clinical features are diverse since PND can affect any part of the nervous system. To provide some uniformity in clinical diagnosis, diagnostic criteria were proposed in 2004 for definite and probable PND (Table 1). These criteria provide a useful approach to diagnosis, but many patients will fail to meet the definition of definite PND, and diagnostic uncertainty remains. This review should help the clinician to better recognize and manage the neuromuscular manifestations of PNDs.

CLINICAL SPECTRUM OF PARANEOPLASTIC NEUROMUSCULAR DISORDERS

Many of the most familiar PNDs are disorders of the central nervous system, such as limbic encephalitis and paraneoplastic cerebellar degeneration. However, peripheral nervous system (PNS) paraneoplastic syndromes are more common than the central ones. Any level of the PNS may be affected from the muscle to the anterior horn cell.

Myopathy

Disorders of muscle are common in cancer patients, although myopathies generally are considered separately from the more typical PNDs discussed below. Many patients with an established diagnosis of cancer develop diffuse muscle atrophy and weakness as part of their general catabolic state. This cachectic myopathy is characterized by type II fiber atrophy.

Patients with inflammatory myopathies, especially dermatomyositis, have an increased risk of malignancy. Estimates vary, but larger studies in Scandinavia indicate that more than 20% of patients with dermatomyositis will have malignancy. The most common malignancies are gastrointestinal (including pancreatic cancer), ovarian, lung, and non-Hodgkin lymphoma. As of now, there are no specific clinical or serological findings that predict the presence of malignancy in patients with inflammatory myopathy. Some patients with cancer develop a more acute and severe paraneoplastic necrotizing myopathy.
kinase (MuSK) antibodies are highly unlikely to have thymoma. Also, patients with MG that are seropositive for muscle specific receptors (AChRs) at the neuromuscular junction cause the disease and can be detected in the serum in about 85% of MG patients. MG is considered in this discussion of PNDs because up to 15% of patients with MG have thymoma. In other words, cancer is unlikely in patients with limited ocular MG or seronegative MG. In patients with generalized AChR antibody seropositive MG, high levels of receptor-modulating antibodies and striated muscle antibodies (such as Titin) should also increase the concern for thymoma.\(^2\)

In LEMS, antibodies against P/Q-type voltage-gated calcium channels (VGCCs) on the motor nerve terminal lead to inefficiency of neuromuscular transmission. LEMS is a PND associated with SCLC in about 60% of adult patients. Patients with paraneoplastic LEMS usually present after age 40 with complaints of generalized weakness and fatigue. The clinical presentation of LEMS differs from MG in that ocular symptoms are uncommon, and LEMS patients have reduced or absent tendon reflexes. When LEMS is associated with SCLC, features of other neurological syndromes may coexist, and other paraneoplastic antibodies may be detected in addition to calcium channel antibodies.

Autoimmune neuromyotonia (NMT, or Isaac’s syndrome) is a disorder of peripheral nerve hyperexcitability. Patients present with diffuse muscle twitching (fasciculations and myokymia) which also may be associated with muscle stiffness, weight loss, and hyperhidrosis. NMT is discussed with neuromuscular junction disorders since the increased muscle activity is thought to originate in the distal motor nerve terminal. NMT is a paraneoplastic manifestation of SCLC or thymoma in about 15% of cases. When NMT occurs in association with features of encephalitis (memory loss, behavior changes, and seizures) or autonomic neuropathy, a paraneoplastic cause is more likely.

It is common practice to obtain a contrast-enhanced computed tomography (CT) scan of the chest at least once after making a diagnosis of MG, LEMS, or NMT. Patients with cancer risk factors or constitutional symptoms may require additional imaging if initial scans are normal.

### Paraneoplastic Peripheral Neuropathy

Signs and symptoms of a peripheral sensorimotor neuropathy (numbness in the feet and fingers or distal weakness) are very common in cancer patients. Some peripheral neuropathies result from nutritional deficiencies or effects of chemotherapeutic agents. However, neuropathy may present well in advance of the cancer diagnosis and is arguably the most common PND. One study estimated that 4.5% of patients with unexplained adult-onset axonal sensorimotor neuropathy have a malignancy.\(^1\) The exact incidence of paraneoplastic peripheral neuropathy, however, remains uncertain. In the majority of cases, the characteristics of a paraneoplastic peripheral neuropathy are those of a mixed sensory and motor length-dependent axonal neuropathy indistinguishable from other nonparaneoplastic neuropathies commonly encountered in the neurology or physical medicine and rehabilitation clinic. A few clinical features should increase the suspicion of a PND. The onset of paraneoplastic peripheral neuropathy tends to be more rapid with progression of symptoms, signs, and electrophysiological changes over weeks or months. Pain is typical. Analysis of cerebrospinal fluid (CSF) may show mild abnormalities, such as increased protein concentration and a mild lymphocytic pleocytosis.

Peripheral neuropathy has been associated with a number of
cancers (small-cell and non–small-cell lung cancer, breast cancer, and thymoma) and with several autoantibody markers (Table 2). However, antibody studies are negative in many patients with paraneoplastic peripheral sensorimotor neuropathy. One unique association of paraneoplastic neuropathy is worth special attention. Patients with osteosclerotic myeloma often develop a paraneoplastic peripheral neuropathy, sometimes associated with other features of the POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome. A radiological bone survey may reveal a sclerotic bone lesion and direct the clinician to this diagnosis.

**Sensory Neuronopathy**

Progressive neuropathy that exclusively affects the sensory nerves has been termed pure sensory neuropathy, sensory ganglionopathy, or sensory neuropathy. This disorder is more classically recognized as a PND, although only about 20% of cases of sensory neuropathy prove to associated with cancer. The remainder are either idiopathic or are associated with systemic autoimmune disease (notably Sjögren’s syndrome) or toxin exposure (including chemotherapy agents). Initial symptoms may commence in the upper or lower extremity and consist of distal pain, numbness, and paresthesias, which can be asymmetric. Because of marked loss of proprioception, clumsiness and gait unsteadiness develop (sensory ataxia). With the eyes closed, the loss of balance and coordination becomes much worse (Romberg’s sign), and slow wandering movements of the digits or limbs (pseudoathetosis) may be observed. Muscle stretch reflexes usually are absent. Often, the disorder progresses relentlessly over weeks or months and leads to significant disability. Because of profound sensory loss, the patient may be unaware of serious injuries to the extremities. Any of several paraneoplastic antibodies may be found, but the typical correlation is with the type 1 antineuronal nuclear antibody (ANNA-1, or anti-Hu antibody) and SCLC. The neurological syndrome usually precedes the diagnosis of cancer, and the detection of cancer may be delayed by over a year despite intensive surveillance.

**Autonomic Ganglionopathy**

Prominent autonomic symptoms can occur in combination with one of the recognized paraneoplastic syndromes (notably with LEMS or with limbic encephalitis), but autonomic neuropathy can be the sole manifestation of PND. Paraneoplastic autonomic neuropathy can manifest as subacute panautonomic neuropathy with symptoms of neurogenic orthostatic hypotension, anhidrosis, dry mouth, impotence, and gastrointestinal dysmotility. Paraneoplastic enteric neuropathy, a limited presentation, produces severe gastrointestinal dysmotility without other autonomic features. These patients present with nausea, early satiety, bloating, abdominal pain, constipation, and resultant weight loss. In severe cases, even fluid intake may be compromised, leading to dehydration. Imaging studies show dilated loops of bowel, and motility studies reveal delayed gastric emptying, diffuse intestinal hypomotility, and absent or incoordinated motor complexes. Such patients initially may be evaluated for bowel obstruction, but endoscopy and exploratory laparotomy fail to identify a cause.

The time course of paraneoplastic autonomic or enteric neuropathy varies from acute autonomic failure to a more insidious onset over several months. Autonomic function testing demonstrates the autonomic deficits but does not differentiate paraneoplastic autonomic neuropathy from other causes of dysautonomia. A variety of autoantibody markers have been associated, most commonly ANNA-1 antibody in association with SCLC. Dysautonomia also may be encountered in association with other tumors, including thymoma.
Paraneoplastic Radiculoplexopathy

Occasionally, proximal nerves and nerve roots are affected prominently in a paraneoplastic neuropathy. Patients present with asymmetric pain and weakness in one or more limbs which can be clinically indistinguishable from other more common forms of radiculoplexopathy (such as diabetic amyotrophy). The lumbosacral plexus more frequently is involved than brachial plexus. As with other PNDs of the PNS, CSF studies often show mild and nonspecific abnormalities. In such cases, studies should be performed to evaluate for the possibility of direct involvement of the plexus or nerve roots by malignancy (from solid or meningeal metastases).

Paraneoplastic Motor Neuronopathy

Even among PNDs which are rare as a group, the syndrome of pure motor neuropathy or motor neuron disease is uncommon. Paraneoplastic motor neuron disease has been reported in association with ovarian, breast, renal, and lung cancers in small numbers of cases. The clinical presentation is progressive painless weakness of the limbs with relative sparing of bulbar muscles. The disorder generally is limited to lower motor neurons, producing a flaccid weakness with areflexia and providing differentiation from amyotrophic lateral sclerosis (ALS). Occasionally, signs of upper and lower motor neuron degeneration may occur in a patient with a new or recent diagnosis of cancer. Although paraneoplastic motor neuron disease should be considered in these cases, it most probably represents an unfortunate coexistence of cancer and ALS.

ELECTROPHYSIOLOGICAL DIAGNOSIS

Nerve conduction studies and needle electromyography (EMG) are very useful to characterize the neuromuscular disorder, but these techniques do not help distinguish paraneoplastic syndromes from nonparaneoplastic ones. For example, LEMS is characterized by normal sensory nerve responses, low-amplitude compound muscle action potential (CMAP) amplitudes, a decremental response to low-frequency repetitive stimulation, facilitation of CMAP amplitude with high-frequency stimulation (or immediately after brief exercise), and prominent motor unit potential variability. These findings help establish the diagnosis but do not differ between patients with cancer and those without. Patients with paraneoplastic sensory neuronopathy have normal CMAP responses and low-amplitude or absent sensory responses (that may be asymmetrically affected). Twenty percent of patients with this pattern have a paraneoplastic sensory neuronopathy, but most have sensory neuropathy of another cause.

Likewise, there are no definitively characteristic histological features of PNDs on muscle and nerve biopsy, but these studies may be important to investigate for other diagnoses (i.e., vasculitis, amyloidosis, etc.)

SEROLOGICAL DIAGNOSIS

Because PNDs usually predate the diagnosis of cancer, diagnosis depends on clinical suspicion. Analysis of CSF may be normal or show only mild lymphocytic pleocytosis and elevated protein. Oligoclonal bands and increased CSF immunoglobulin G synthesis rate are seen in a minority of cases. The advent and expansion of testing for paraneoplastic neurological autoantibodies has been a great help in diagnosing PNDs (Table 2). Several commercial laboratories provide this service. It is useful to consider two different types of paraneoplastic autoantibodies, since the clinical implications differ significantly.

Ion Channel Antibodies

One group of ion channel antibodies are antibodies directed against cell surface antigens, including neuronal ion channels (Table 2). Ion channel antibodies usually are very sensitive and quite specific for a particular neurological disorder, but they are not highly predictive of malignancy. Antibodies against neuronal P/Q-type VGCCs are found in nearly all patients with LEMS, but only about 60% of adult patients with LEMS have cancer. Antibodies against muscle AChRs are found in more than 80% of patients with MG, but only 15% have thymoma. Hence, the antibody is a marker of the disease but not a marker of cancer. Other PNDs associated with ion channel antibodies include neuropathy, autoimmune autonomic neuropathy, encephalitis, and cerebellar ataxia.

Autoantibodies have direct access to ion channels since these are integral membrane proteins with an extracellular domain. Studies in animal models have shown that the antibodies bind and interfere with synaptic function or cause internalization and degradation of the ion channels. In many cases, the antibodies have been proven to be directly pathogenic; injection of purified antibodies into experimental animals reproduces key features of the disease. Removal of the antibodies using plasmapheresis improves the clinical symptoms.

Paraneoplastic Antibodies Against Intracellular Antigens

In contrast, neuronal nuclear and cytoplasmic antibodies are highly specific for the presence of cancer and also predictive of the cancer type but probably are not directly pathogenic. These antibodies are important as surrogate markers of a specific immune response to cancer and may be detected in the serum or CSF. For PNS disorders, the most relevant antibodies are the ANNA-1 antibody, the collapsing-response-mediator protein 5 (CRMP-5) (anti-crossveinless-2 [CV2]) antibody, and the sex determining region Y-box 1 (sox-1) antibody. However, since it is difficult to predict which antibody may be present in an individual patient, it is recommended to request testing for a broad panel of paraneoplastic antibodies.

The ANNA-1 antibody is the most frequently encountered paraneoplastic antibody. ANNA-1 specifically recognizes a 35-40 kDa family of neuronal nuclear RNA-binding proteins and labels the nuclei (and to a lesser extent the cytoplasm) of all neurons. Characteristically, ANNA-1 also binds to peripheral neurons in autonomic and dorsal root ganglia. Nearly 90% of patients with ANNA-1 have SCLC. Patients with antibodies against CRMP-5 antibody are highly likely to harbor either SCLC or thymoma. Sox-1 antibodies (also known as antiglial nuclear antibody, AGNA) are predictive of SCLC. In particular, 64% of
patients with LEMS and SCLs had sox-1 antibodies in addition to calcium channel antibodies, while none of the patients with nonparaneoplastic LEMS had the sox-1 antibody.\textsuperscript{23}

Finding one of the neuronal nuclear or cytoplasmic antibodies in a patient with a neurological syndrome should mandate a thorough evaluation for occult malignancy and close oncological followup if cancer is not detected on the initial search. The antibody specificity helps direct the search for cancer by predicting the most likely cancer. Unfortunately, even comprehensive testing for all known paraneoplastic antibodies lacks the sensitivity to completely exclude a PND.

**PATHOPHYSIOLOGY**

Several lines of evidence support the designation of PNDs as autoimmune disorders of the nervous system. The targets for most of the paraneoplastic antibodies are so-called “onconeural antigens,” proteins shared by both tumor cells and neurons. Both T-cell and antibody-mediated processes have been implicated. The relative contributions of cell-mediated and humoral mechanisms to neural damage in PNDs differ among different syndromes.

In general, antibodies are more likely to play an important pathophysiological role in syndromes associated with antibodies against cell surface antigens.\textsuperscript{4} Examples include VGCC antibodies in LEMS, AChR antibodies in MG, and N-Methyl-D-aspartate (NMDA) receptor antibodies in limbic encephalitis. These patients generally have more potential for recovery because the antibodies cause reversible loss of synaptic function rather than neuronal damage.

In cases where the paraneoplastic antigens are located in the nucleus or cytoplasm, a pathogenic role for the corresponding antibodies has not been established; the specific antigens are intracellular and not readily accessible in living neurons.\textsuperscript{23} In these cases, indirect (but persuasive) evidence points to cytotoxic cell-mediated immunity as the main mechanism.\textsuperscript{2,24,25} Pathological studies in PND cases may show infiltration of the tumor as well as targeting of the nervous tissue by inflammatory cells.\textsuperscript{59} In the PNS, inflammatory infiltrates of lymphocytes can be seen in the dorsal root ganglia (in cases of paraneoplastic sensory neuropathy) or in the myenteric plexus (in cases of paraneoplastic enteric ganglionopathy).\textsuperscript{3} This cytotoxic immune attack results in neuronal destruction and irreversible clinical deficits.

**DIAGNOSIS AND TREATMENT CONCEPTS**

The diagnosis of PND can be challenging since these disorders are rare and present in a myriad of ways. Important clinical clues that should raise the suspicion for PND include: (1) subacute and progressive course, (2) multifocal pattern of neurological deficits (especially when part of the clinical picture fits one of the classic central or peripheral paraneoplastic syndromes), and (3) constitutional symptoms or cancer risk factors (i.e., unexplained weight loss, long history of smoking). If there is a high level of clinical suspicion for a PND, the clinician should proceed with cancer screening, even if serological tests are unrevealing.

**Oncological Diagnosis**

High resolution contrast-enhanced CT scan of the chest, abdomen, and pelvis will uncover underlying tumor in a large number of patients. Complete blood counts and cytology should also be performed. If routine CT imaging is negative, in face of high clinical suspicion or the presence of a predictive antibody, whole body fluorodeoxyglucose (FDG) positron emission tomography (PET) should be considered. Several prospective and retrospective studies of patients with PNDs have been reported. In patients with well-characterized autoantibodies in whom conventional imaging was negative for underlying malignancy, FDG-PET showed an abnormality in 37-83%.\textsuperscript{30,18,12} However, a tissue diagnosis of cancer was not possible in many cases with positive FDG-PET imaging suggesting that false-positives may occur. The current consensus is that FDG-PET should be reserved for patients with high likelihood of PNDs (usually those that are seropositive for a predictive paraneoplastic antibody) in whom conventional imaging fails to identify the tumor or where imaging results are equivocal. If no cancer is found initially, repeat cancer screening should be scheduled (3-month intervals for a year is often recommended).

**Treatment and Prognosis**

Because PNDs are quite rare, very few formal therapeutic studies have been performed. In many cases, neurological symptoms respond poorly to current treatments. When approaching a patient with a PND, the clinician’s primary goals are to: (1) identify and eradicate the underlying malignancy as soon as possible, (2) identify those PNDs that are most likely to respond to immunotherapy, (3) counsel the patient and family about the nature of the PND including the uncertainties and goals of treatment, and (4) initiate a treatment plan.

When found, tumors tend to be small and show only limited local metastasis. Therefore, cancer may be relatively more amenable to treatment.\textsuperscript{14,17} In addition to preventing cancer progression, treatment can help eliminate the neoplasm as a stimulus for ongoing autoimmunity, and the immunosuppressive effects of chemotherapeutic agents may help dampen the immune response. In the case of osteosclerotic myeloma, radiation treatment may result in improvement of the neuropathy, perhaps by eliminating the malignant cells that are producing pathogenic antibodies.\textsuperscript{5}

Immunomodulatory therapy can be considered in cases where a malignancy has not been identified, in cases where oncological treatment has been completed, or in conjunction with cancer treatment. PNDs where antibodies are directed against cell surface antigens (i.e., LEMS, MG, and NMT) are most responsive to immunomodulatory treatment. In these syndromes, antibodies may produce a functional neuronal deficit rather than irreversible neuronal damage, so treatments aimed at reducing circulating levels of pathogenic antibodies (e.g., intravenous immunoglobulin [IVIg] and plasma exchange [PE]) are particularly effective.

For PNDs associated with cell-mediated immunity, data on treatment response largely is based on small retrospective studies and case reports (corticosteroids, IVIg, PE, rituximab, and cyclophosphamide). In earlier reviews of available retrospective case series, only 33 cases of effective treatment...
were documented out of 259 reported cases. A few systematic prospective series have been conducted, using IVIg, PE, and/or cyclophosphamide. From these studies, it appears that immunomodulatory treatment may provide a useful stabilization of disability in patients who are still ambulatory, but much of the neurological deficit is irreversible. Immunosuppressive agents probably are required in most cases. Patients with PNDs affecting the peripheral, as opposed to central, nervous system tend to have a better outcome.

**SUMMARY**

Although uncommon, PNDs frequently affect the PNS. The clinical syndromes are diverse, therefore PNDs should be considered frequently in the differential diagnosis. Serological testing is very valuable but not highly sensitive. Clinicians should understand the implications of different types of paraneoplastic antibodies. PNDs are treatable, but, in some cases, the goal of therapy is to prevent progression of neurological deficits rather than clinical recovery.

**REFERENCES**

Plexopathy and Radiculopathy in Cancer

Kurt A. Jaeckle, MD
Professor of Neurology and Oncology
Department of Neurology and Oncology
Mayo Clinic Florida
Jacksonville, Florida

INTRODUCTION

Neoplastic (carcinomatous tumor) plexopathy and radiculopathy often occur in the setting of widespread metastases from active systemic cancer. Disorders of the brachial and lumbosacral plexus are the most frequently encountered in clinical practice. Radiculopathy in cancer patients usually follows metastases to the vertebrae or ribs, and with leptomeningeal metastases.

NEOPLASTIC PLEXOPATHY

Cervical Plexopathy

Cervical plexopathy is the least common of the neoplastic plexopathies, and the incidence has not been well described. Generally, the neoplasms invade the plexus directly from the neck, or indirectly following metastatic spread to regional lymph nodes, soft tissues, or bony structures. The most common tumors are squamous cell carcinoma, lymphoma, and breast and lung adenocarcinomas. Patients with cervical plexopathy usually present with pain in the neck, pharynx, or shoulder. Often, the pain is exacerbated by cough, neck movements, or swallowing. The pain may be radicular, dull and aching, or causalgic in quality. Patients often complain of a vague pressure and numbness over the anterior neck. There can be dizziness or even syncope with neck movements. Tumor may involve the spinal accessory nerve (cranial nerve XI), resulting in weakness of the trapezius and sternocleidomastoid muscles. Phrenic nerve involvement, although uncommon, may be a part of the presentation, producing positional dyspnea, via paralysis of the hemidiaphragm. This diagnosis can be confirmed by chest radiographs. It is important to remember that these patients are at relatively high risk to develop concomitant or future cervical epidural extension.

In patients with prior tumor resection and lymph node removal, the clinical and needle electromyographic (EMG) evaluations can be challenging, as one must distinguish surgically-induced denervation from that due to tumor invasion to help identify the appropriate location for radiation. Following resection of head and neck tumors and regional nodes, usually there is sensory loss in the distribution of the superficial branches of the greater auricular nerve, producing numbness in the pre-auricular area, anterior neck, and submandibular area, and a temporal relationship of the prior dysfunction to the surgical procedure.

Brachial Plexopathy

Brachial plexopathy perhaps is the most common plexopathy encountered in clinical practice. Common tumors associated with this complication are delineated in Table 1. In cancer hospitals, neoplastic brachial plexopathy has accounted for 0.43% of neurologic consultations. Metastatic tumors of the lung or breast most often are associated with this condition. Up to 5% of breast cancer patients develop symptomatic plexopathy at 5 years from diagnosis. Typically, tumor may invade the inferior trunk and medial cord of the lower plexus (Pancoast syndrome), producing numbness along the ulnar border, hand intrinsic muscle...
weakness, and a palpable supraclavicular or axillary mass. The upper plexus more typically is involved in patients with head and neck neoplasms, thyroid malignancies, or lymphomas. Metastases to scattered lymph nodes within the plexus can produce a mosaic pattern of involvement of the trunks and cords, noted clinically or on needle EMG.

Pain initially is present in 75% of patients, and usually it is located in the shoulder and axilla. With lower plexus involvement, radicular pain and weakness often follows the C8-T1 distribution, via involvement of the inferior trunk. Approximately one-fourth of patients have an associated Horner’s syndrome. These patients are at high risk to develop associated epidural extension of tumor.

**Lumbosacral Plexopathy**

The frequency of lumbosacral plexopathy in cancer patients is 0.71%. The most commonly associated tumors are colorectal, prostate and gynecologic malignancies, lymphomas, and retroperitoneal sarcomas (Table 1). Usually, tumor invades the lumbosacral plexus by direct extension from the pelvis or abdomen, or following spread from local lymph node metastases, most common with breast carcinoma. The plexopathy is present at the time of initial cancer presentation in 15% of patients.

Clinical syndromes of the upper plexus (L1-L4), lumbosacral trunk (L4-L5), and lower plexus (S1-S4) have been described. Plexopathy usually is unilateral but is bilateral in 25% of cases. Pain usually is present early in the course (98% of patients), and the absence of pain should prompt consideration of alternative diagnoses. Pain initially is intermittent, but it soon becomes constant, dull, and aching, with superimposed sharp components. The pain may be exacerbated by weight bearing, exercise, valsalva, or manifest in the supine position. Weakness and sensory complaints eventually develop in most patients. The most common clinical findings are leg weakness (86%), sensory loss (73%), reflex loss (64%), and leg edema (47%).

*Table 1. Neoplasms commonly associated with plexopathy*  

<table>
<thead>
<tr>
<th>Cervical plexus*</th>
<th>Brachial plexus (%)</th>
<th>Lumbosacral plexus (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck squamous</td>
<td>Lung carcinoma (37)</td>
<td>Colorectal carcinoma (20)</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>Breast carcinoma (32)</td>
<td>Sarcoma (16)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>Lymphoma (8)</td>
<td>Breast carcinoma (11)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Sarcoma (5)</td>
<td>Lymphoma (9)</td>
</tr>
<tr>
<td>Other tumors</td>
<td>Other tumors (18)</td>
<td>Cervix carcinoma (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other tumors (37)</td>
</tr>
</tbody>
</table>

*Frequency of these tumors in association with cervical plexopathy not determined  
Modified from Jaeckle KA.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) increasingly has been utilized to confirm the suspicion of neoplasm within the plexus, in some cases obviating the need for biopsy (Fig. 3). Nearly 75% of breast cancer patients with clinical evidence of neoplastic brachial plexopathy, have FDG uptake within the plexus.

The pattern of denervation on needle EMG can help direct neuroimaging studies and even radiation treatment. Needle EMG often reveals patchy active denervation and reinervation. The needle EMG/nerve conduction velocity (NCV) pattern can be difficult to distinguish from polyradiculopathy, due to the predominant proximal axonal pattern in both conditions. It is not unusual for the needle EMG to show more extensive denervation...
than clinically suggested, or for it to detect unexpected bilateral plexus involvement, which occurs in approximately 15-20% of patients. Generally, the pattern of active denervation facilitates the distinction from nerve root or leptomeningeal involvement. For example, paraspinal denervation is less common with plexus involvement, and bilateral, asymmetrical denervation is more common with leptomeningeal disease. One must remember that leptomeningeal, root, and plexus involvement can be present in the same individual, making the needle EMG interpretation challenging.

**Differential Diagnosis**

In previously treated patients, radiation-induced plexopathy is the most common differential consideration (Fig. 4A-B). Other possibilities include plexopathy resulting from regional intra-arterial chemotherapy, hemorrhage, infarction, infections, and paraneoplastic plexopathy. The overall frequency of radiation plexopathy in treated patients is approximately 1.8-4.9%. At 5-year followup, radiation plexopathy was present in 2% of patients with stage III breast cancer, following treatment with 4,500-5,000 cGy to the chest wall and local lymphatics. The time from radiotherapy and development of plexopathy ranges from 3 months to 20 years, with a median of 1.5 years, and is more frequent at doses greater than 5,000 cGy. Many radiation oncologists believe that the risk may decrease with modern application of intensity-modulated radiotherapy and hypofractionated dosing regimens. Although unproven, it has been postulated that chemotherapy may potentiate the development of radiation plexopathy. Clinical and needle EMG features that help distinguish radiation plexopathy from tumor plexopathy are listed in Table 2. Radiation plexopathy often presents with dysesthesias and numbness, rather than pain, and often there is lymphedema. More than half of the patients eventually develop weakness, numbness, paresthesias, and pain. Radiation brachial plexopathy has been reported to primarily affect the upper plexus but any area of the plexus may be involved. Radiation-induced lumbosacral plexopathy most frequently develops between 12 months and 5 years following treatment, with a range from 1 month to 31 years. Sympathetic dysfunction and bilateral lumbosacral plexopathy is more common with radiation than with neoplastic involvement. Local skin telangiectasias and atrophy, subcutaneous induration, and lymphedema support the diagnosis.

Imaging procedures may disclose local fibrotic changes in the region (e.g., apex of the lung, necrosis of the clavicle, ribs or shoulder, and pericardial fibrosis). Approximately 60% of patients with radiation-induced plexopathy will show myokymia on needle EMG, which is uncommon with neoplastic plexopathy. Similarly, the lack of a mass or plexus enhancement on MRI and the lack of FDG uptake in the plexus region on PET imaging support the diagnosis of radiation plexopathy. The treatment of radiation-induced plexopathy is symptomatic. Most patients experience a slow but steady progressive loss of motor and sensory function, although occasionally the condition will inexplicably stabilize. Hyperbaric oxygen, anticoagulants, and antioxidants have been tried to help delay the progression, but there is no level I or II evidence of benefit of these approaches. Nerve transfer and nerve reconstruction has been utilized in select individuals who appear in to be permanent remission from their cancer.
Treatment of Neoplastic Plexopathy

The most commonly employed treatment for neoplastic plexopathy is radiotherapy. Radiation produced subjective improvement in symptoms (primarily pain) in 85% of patients with lumbosacral plexopathy and objective improvement in 48%, defined as neurologic improvement or reduction in measurable tumor. The average duration of response, however, was only 4 months. Objective reduction in tumor size by CT has been observed in one-third of patients. In breast cancer patients, 86% achieved partial or complete remission of pain or neurologic deficits, with an 8-month median duration (radiation with or without chemotherapy or hormonal therapy). Some patients with lymphomatous plexopathy will respond to chemotherapy alone, but radiation to the involved plexus is a reasonable consideration for patients who have acute, severe pain or rapidly progressive weakness.

Other pain control measures often may include opiate analgesics, infusion pumps, local and regional blocks, transcutaneous nerve stimulators, sympathectomy, and rhizotomy. Although of unproven benefit, attempts have been made to treat dysesthesia and causalgia with tricyclic antidepressants, gabapentin, lamotrigine, carbamazepine, topirimate, baclofen, valproic acid, or phenytoin. Selective application of lidocaine dermal patches to local areas of pain or causalgia may provide temporary benefit without adding sedative effects. Physical therapy and other adaptive strategies are warranted early in the course of neoplastic plexopathy in order to prevent painful contractures, compressive neuropathies, respiratory or urinary tract infections, pressure sores, and deep venous thromboses. Lymphedema may be treated with compressive devices and elevation.

NEOPLASTIC RADICULOPATHY

In general, radiculopathy in cancer patients results from invasion or compression by neighboring metastatic tumor. The site of nerve root involvement can be intradural (leptomeningeal metastasis) or extradural (following metastasis to the vertebral bones, proximal ribs, sacrum, or lymph nodes or soft tissues within the paravertebral gutter). Often, more than one root is involved.

Approximately 10% of cancer patients develop symptomatic vertebral metastases, and more than one area of involvement is present in more than 50% of patients. The vertebral column is the most common location of bony metastasis, eventually occurring in as many as 70% of cancer patients. Of these, approximately 10-20% will be symptomatic, usually presenting with radicular pain, focal lower motor neuron distribution weakness, paresthesias, or numbness. Radicular symptoms have been reported as the presenting manifestation of cancer in up to 20% of patients. The most common tumors to metastasize to bone are breast, lung, prostate, and renal adenocarcinomas, thyroid carcinoma, melanoma, lymphoma, and multiple myeloma. Although metastases to the lumbar spine are more common overall, thoracic metastases are more commonly symptomatic.

Occasionally, patients will develop radiculopathy following rib metastases. In contrast to patients with vertebral metastases, patients with rib metastases usually have pain or numbness in one nerve root distribution (unless multiple ribs are involved or concomitant vertebral metastases are present). The patient may point out localized tenderness or swelling over the involved rib, and (gentle) pressure over this area may reproduce the pain.

Patients also may develop radiculopathy from metastases to neighboring soft tissues. Paravertebral gutter invasion is more frequent in patients with lung primary carcinoma or metastases with lymphoma. Retroperitoneal involvement within the pelvis or abdomen is more frequent in patients with prostate and gynecologic malignancies, lymphoma, and sarcoma. Tumor sometimes can be identified tracking back along the epineurium of one or more specific roots. Rarely, direct metastases to individual nerve roots have been described in patients with carcinoma of the breast and lung, leukemia, and melanoma. Breast and prostate adenocarcinoma and lymphoma may metastasize to the dura,
affecting exiting nerve roots, even in the absence of concomitant leptomeningeal invasion.

Intradural involvement of nerve roots generally is observed in patients with leptomeningeal metastases, which occur in approximately 3-8% of patients with cancer. Radicular pain is present in more than 50% of these patients. Neoplastic meningitis is observed most frequently in patients with breast and lung carcinomas, melanoma, hematologic malignancies, and primary central nervous system tumors such as medulloblastoma, primitive neuroectodermal tumors, and germ cell malignancies. Needle EMG can help distinguish the bilateral polyradicular pattern typically observed in neoplastic meningitis from isolated root involvement or lateralized denervation, the latter more common with plexopathy.

The pain with cancer radiculopathy is often severe, sharp, and unrelenting. It often is described as shooting or lancinating, superimposed on a dull ache, with or without causalgic qualities. Cramping or soreness may be present in the muscles innervated by the specific root(s). Localization can be guided by the clinical pattern of sensory and reflex loss, lower motor neuron weakness, atrophy, and fasciculations. These findings will often facilitate the choice and focus of the neuroimaging and electrophysiologic procedures.

**Diagnosis**

Appropriate imaging with high-resolution enhanced MRI or CT often will identify the responsible tumor mass in the area predicted by the symptoms or examination. The diagnosis is further supported by an FDG-PET scan, which optimally shows high glucose uptake within the suspect area. Surgical confirmation may be indicated if the complication represents the initial presentation of cancer, or if it is the first or only area of suspected relapse following prior successful treatment. Electrophysiologic procedures can be valuable, in that they may disclose areas of active denervation suggesting recent and ongoing involvement, and, as with plexopathy, they may disclose more widespread involvement than is suggested by the imaging procedures. Needle EMG also may help distinguish radiculopathy from plexus and leptomeningeal involvement or radiation-induced radiculopathy or plexopathy (Table 2). Optimal patient management results from open communication between specialists, who combine the clinical, electrophysiologic, and radiographic abnormalities to arrive at the best treatment plan.

**Differential Diagnosis**

Radiculopathy in the cancer patient also may result as a delayed complication of radiation or after intra-arterial regional chemotherapy. Usually, there is a history of radiation years earlier for symptomatic vertebral metastases. The clinician should suspect this complication when imaging studies fail to show evidence of a mass in the suspected area of involvement based on the distribution of radicular symptoms and signs. The diagnosis is supported if physical examination findings suggest sensitivity to the effects of prior radiotherapy (e.g., robust thickening and discoloration of skin within the treatment field). With plexopathy, imaging may show fibrosis of neighboring soft tissues or osteonecrosis of bone, and FDG-PET imaging usually is negative. Radiculopathy due to chemotherapy, albeit rare, generally has occurred following regional intra-arterial cisplatin or Adriamycin for bulky tumors. Patients with myeloid dysplasias or postautologous bone marrow transplant can develop polyradiculopathy or polyradiculitis (the latter with enhancing nerve roots on MRI) without a discernable cause; generally these have been considered autoimmune or paraneoplastic in nature. Finally, nerve roots may be compromised during challenging surgical extractions of invasive, adherent tumors within the region. Generally, these radiculopathies are evident within the first days following the procedure.

**Treatment**

As with plexopathy, the primary interventions for neoplastic radiculopathy are supportive and directed at pain management and prevention of complications of weakness or immobility. Local radiotherapy to the area of involvement may produce symptomatic benefit. Systemic or intrathecal chemotherapy may be palliative, in particular in patients with hematologic malignancies.

### Table 2. Clinical features of neoplastic and radiation-induced plexopathy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Neoplastic</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial common symptoms</td>
<td>Pain</td>
<td>Paresthesias, weakness</td>
</tr>
<tr>
<td>Timing of pain development</td>
<td>Early, severe</td>
<td>Later in course</td>
</tr>
<tr>
<td>Extremity edema</td>
<td>Occasional</td>
<td>More common</td>
</tr>
<tr>
<td>Area of plexus affected</td>
<td>Often lower plexus</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Brachial</td>
<td>Lower, usually unilateral</td>
<td>Diffuse, often bilateral</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>Reasonably frequent</td>
<td>Unusual</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>Not present</td>
<td>Common</td>
</tr>
<tr>
<td>Local radiographic evidence of radiation</td>
<td>Frequent</td>
<td>Unusual</td>
</tr>
<tr>
<td>Rectal Mass (lumbosacral plexus)</td>
<td>Unusual</td>
<td>Often present</td>
</tr>
<tr>
<td>Myokymia (EMG)</td>
<td>Present</td>
<td>Usually present</td>
</tr>
<tr>
<td>Nerve enhancement (MRI)</td>
<td>Localized FDG uptake</td>
<td>Usually absent</td>
</tr>
<tr>
<td>PET scan</td>
<td></td>
<td>Usually negative</td>
</tr>
</tbody>
</table>

EMG = electromyography, FDG = fluorodeoxyglucose, MRI = magnetic resonance imaging, PET = position emission tomography

*Modified from Jaeckle.*

---

**PLENARY: NEUROMUSCULAR COMPLICATIONS OF CANCER AND ITS TREATMENT**

**Table 2. Clinical features of neoplastic and radiation-induced plexopathy**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Neoplastic</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial common symptoms</td>
<td>Pain</td>
<td>Paresthesias, weakness</td>
</tr>
<tr>
<td>Timing of pain development</td>
<td>Early, severe</td>
<td>Later in course</td>
</tr>
<tr>
<td>Extremity edema</td>
<td>Occasional</td>
<td>More common</td>
</tr>
<tr>
<td>Area of plexus affected</td>
<td>Often lower plexus</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Brachial</td>
<td>Lower, usually unilateral</td>
<td>Diffuse, often bilateral</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>Reasonably frequent</td>
<td>Unusual</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>Not present</td>
<td>Common</td>
</tr>
<tr>
<td>Local radiographic evidence of radiation</td>
<td>Frequent</td>
<td>Unusual</td>
</tr>
<tr>
<td>Rectal Mass (lumbosacral plexus)</td>
<td>Unusual</td>
<td>Often present</td>
</tr>
<tr>
<td>Myokymia (EMG)</td>
<td>Present</td>
<td>Usually present</td>
</tr>
<tr>
<td>Nerve enhancement (MRI)</td>
<td>Localized FDG uptake</td>
<td>Usually absent</td>
</tr>
<tr>
<td>PET scan</td>
<td></td>
<td>Usually negative</td>
</tr>
</tbody>
</table>

EMG = electromyography, FDG = fluorodeoxyglucose, MRI = magnetic resonance imaging, PET = position emission tomography

*Modified from Jaeckle.*
REFERENCES

Update on Imaging of the Spine and Plexus in Cancer

Eric Lis, MD
Associate Clinical Attending
Director of Neurointerventional Radiology
Memorial Sloan-Kettering Cancer Center
Assistant Professor of Radiology
Weill Cornell Medical School
New York, New York

Cancer patients with symptoms referable to the spine and the brachial or lumbar plexuses present a unique imaging challenge. Cancer, either primary or metastatic, can involve any portions of the spine or plexuses. In the spine, metastatic disease most commonly involves the epidural space. Intradural disease (i.e., leptomeningeal or intramedullary [spinal cord] metastasis) is less common. In addition, several complications of cancer therapy can affect the spine, sometimes mimicking metastatic disease. Problems that often are unique to cancer patients may be superimposed on more mundane and common processes that can involve any nonmalignant spine, particularly degenerative disease. Similarly, symptoms related to either the lumbosacral or sacral plexus (often described as a plexopathy) can be caused by a variety of conditions. Tumor can arise directly with the neural elements of the plexuses or, secondarily, infiltrate or extrinsically deform the plexuses from disease arising within adjacent structures. As in the spine, the complications of cancer therapy, surgery, radiation, and chemotherapy can result in a plexopathy.

The goal of this discussion is to impart an understanding of fundamental spine and plexus imaging and anatomy to the clinician and to advance their knowledge of the most common lesions involving the spine and plexus in cancer patients. The choice of optimal imaging modalities for evaluation of the spine and plexuses will be discussed. In addition, newer advanced imaging techniques will be introduced and their potential role in the evaluation of cancer patients with symptomatology referable to the spine or plexuses will be reviewed. The diagnosis and treatment of lesions arising in or about the spine and plexuses in the cancer patient require a multidisciplinary approach and, with the proper use of imaging that is fortified by clinical input, will lead to earlier diagnosis, better management options, and ultimately improved neurological, functional, and potentially oncologic outcomes.

BASIC SPINE IMAGING: ANATOMY AND TERMINOLOGY

The spine is best divided up into three anatomic spaces: the epidural, the intradural extramedullary, and the intradural intramedullary (Fig. 1). The first and largest space is the epidural (extradural) space. The epidural space surrounds the thecal sac/dural sac and basically is everything outside of the thecal sac. Metastatic tumors that typically involve the epidural space usually arise within the osseous spine/vertebrae. These are the typical vertebral body metastases that expand into the epidural space and encroach upon the spinal canal and its contents. Less commonly, tumors such as leukemia and lymphoma can involve the epidural space without primary involvement of the osseous spine.

Intradural tumors can be broken down into two basic groups: intradural extramedullary and intramedullary lesions. Intradural extramedullary metastasis, more commonly referred to as leptomeningeal disease, is tumor that secondarily involves the leptomeninges and the subarachnoid (cerebral spinal fluid [CSF]) space. Occasionally, these lesions can be large enough where they extrinsically deform or compress the spinal cord and are potentially confused with epidural disease. Least common is the intramedullary metastasis which is a lesion arising within the substance of the spinal cord.
For practical purposes, one of the best ways to understand the compartments of the spine at the level of the spinal cord and the level of the cord equina is with a postmyelogram computed tomography (CT) scan (Fig. 2A-E). The thecal sac CSF space, which is opacified by contrast, is identified easily. The spinal cord is seen centrally with the nerve route of the cauda equina also easily identify. Recall that the epidural space is everything outside of the opacified thecal sac. This space is occupied predominately by the vertebrae but also includes epidural fat, ligaments, and vascular plexuses. Working inward the next space is the intradural extramedullary space. Thus, for practical purposes, everything between the spinal cord and the dura is the CSF space, which in this case is opacified by contrast. Typically, metastatic disease that involves the meninges of the spine would appear as filling defects or nodules along the surface of the cauda equina or spinal cord. The intradural intramedullary compartment, which basically is the spinal cord, is outlined by the opacified thecal sac. This basic understanding of spinal anatomy is easily applicable to magnetic resonance imaging (MRI).

**DIAGNOSTIC SPINE IMAGING**

The most common imaging modalities that are readily available to cancer patients with symptoms referable to the spine are plain films, CT, MRI, and CT-myelography. Fluorodeoxyglucose (FDG) positron emission tomography (PET) scans have a complimentary role, particularly when obtained in conjunction with a MRI. Bone scans have a limited role.

**Spine Magnetic Resonance Imaging**

MRI is the modality of choice for imaging of the spine in cancer patients. Contraindications to MRI generally include the presence of any metallic material susceptible to magnetic fields. This includes a cardiac pacemaker, implanted cardiac defibrillator, cochlear implant, carotid artery vascular clamp, neurostimulator, insulin or other implanted drug infusion device, bone growth/fusion stimulator, and certain aneurysm clips. MRI currently is the most sensitive and specific imaging modality in evaluating spine tumors.

Adequate imaging of the entire spine can be performed easily with any of the commercially available MRI units. Thorough MRI of the spine usually requires both T1- and T2-weighted images.
obtained in the sagittal plane with selected axial images through regions of interest. Typically, the entire spine can be imaged in an hour or less by using a large enough field of view that essentially divides the spine into upper and lower halves with slight overlap of the lower thoracic spine to ensure complete coverage. Ideally, the part of the spine that is clinically symptomatic should be imaged first just in case the patient is unable to complete the study. Axial images are prescribed as needed.

Figure 3. Magnetic resonance imaging survey of the total spine in the sagittal plane in a patient with esophageal cancer and a typically appearing T3 spinous process metastasis. (A) Fused sagittal T1 upper and lower halves of the spine. (B) Matching postcontrast T1, (C) fast spin echo (FSE) T2, and (D) T2 STIR. Notice the hyperintense dorsal epidural fat especially in the lumbar spine as well as the hyperintense subcutaneous fat, both of which are suppressed on the T2 short tau inversion recovery (STIR) images. Notice that the T3 spinous process metastasis is less conspicuous on the FSE T2 series (C) compared to the T2 STIR series (D).

T1-weighted images provide anatomic definition, marrow detail, and generally a good overview of the spinal column. CSF is hypointense (dark) and fat is hyperintense (bright). Most bone metastasis typically are hypointense on T1-weighted sequences relative to the marrow which is often slightly hyperintense secondary to its fat content in adults. Fast spin echo (FSE) T2-weighted sequences essentially have replaced standard T2-weighted sequences secondary to significantly decreased imaging time. CSF is hyperintense on T2-weighted images with FSE T2 images providing excellent definition of both the spinal cord and CSF spaces. However, bone metastasis often are less conspicuous on FSE T2 images as fat is somewhat hyperintense on FSE T2 images. This can be compensated for by using short tau inversion recovery (STIR) techniques, which result in a fat-suppressed T2 image in which many tumors appear hyperintense to adjacent marrow. STIR techniques also are very sensitive in identifying marrow edema. Most vertebral metastasis usually are hypointense on T1-weighted images and hyperintense on T2-weighted images and also hyperintense (though generally more conspicuous) on T2 STIR images (Fig. 3A-D). Sclerotic metastasis most often are hypointense (dark) on all pulse sequences.

Other pulse sequence that are less common but are occasionally added to spine studies in certain situations include gradient echo (GRE) sequences (which often are useful in identifying blood products) or ultra fast sequences such half NEX single shot FSE T2 sequences (which are useful when patient motion degrades standard images). This type of pulse sequence is able to image the lower or upper half of the spine in the sagittal or axial plane in less than 15 s. Though it comes at cost of lesion conspicuity, it usually provides enough information to exclude any problem requiring immediate intervention.

The use of gadolinium-based contrast agents is useful particularly in the identification of leptomeningeal disease or intramedullary/spinal cord tumors, both which typically enhance as do most osseous metastasis and epidural disease. Gadolinium also may be useful in the evaluation of the postoperative spine to differentiate scar from tumor and for the evaluation of infection (i.e., abscess).

**Spine Plain Films**

Plain films of the spine are readily available but generally a poor screening for metastatic disease. About 30-50% bone destruction is needed before a lytic lesion can be identified on a radiograph. Vertebral compression fractures are identified easily though the degree of canal compromise can be difficult to determine. Plain films can be obtained while weight bearing, possibly identifying deformities or malalignments that otherwise would be undetected in supine nonweight bearing positions required for CT and MRI. In the postoperative patient, plain films are most useful in assessing the alignment of the spine and the structural integrity of the reconstruction hardware.

**Spine Computed Tomography**

Over the last decade the introduction of multidetector helical CT scanners has greatly improved the use of CT as a spine imaging modality. Axial images can be acquired quickly through the entire spine in matter of minutes and reconstructed in even thinner slice
nonionic water-soluble contrast into the subarachnoid space via compression. A myelogram consists of infusion a small amount of Myelography when combined with a postmyelogram CT scan is forefront with myelography. Intradural, and intramedullary compartments were brought to the nerve root or spinal cord compression. The descriptive epidural, diagnostic study of choice for the evaluation of the spine regarding Before MRI, myelography and then CT-myelography was the good at identifying marrow infiltration without bony changes. CT scan is not very sensitivities for sagittal and coronal reformations. An unenhanced CT scan is not very sensitive for the identification of epidural soft tissue tumor, especially when compared to MRI, but it is extremely good at demonstrating lytic or sclerotic bony changes and cortical destruction. Contrast will improve epidural soft tissue conspicuity but is not terribly good in identifying leptomeningeal and intramedullary tumor (Fig. 4A-B). Similarly, CT is not very good at identifying marrow infiltration without bony changes.

**Spine Computed Tomography Myelography**

Before MRI, myelography and then CT-myelography was the diagnostic study of choice for the evaluation of the spine regarding nerve root or spinal cord compression. The descriptive epidural, intradural, and intramedullary compartments were brought to the forefront with myelography.

Myelography when combined with a postmyelogram CT scan is very sensitive in the detection of epidural tumor and spinal cord compression. A myelogram consists of infusion a small amount of nonionic water-soluble contrast into the subarachnoid space via a lumbar puncture or, less commonly, a cervical C1-2 puncture. The intrathecal contrast then is advanced in a controlled fashion throughout the spinal column with fluoroscopic spot images obtained with attention to regions of the spine where the flow of intrathecal contrast is either held up or “blocked,” usually secondary to epidural tumor in cancer patients. A myelogram is almost always followed by a CT scan of the spine, which adds much greater detail and anatomic definition. At the time of the procedure a small amount CSF also is obtained which then can be sent for analysis (particularly cytopathology to determine the presence or absence of neoplastic cells indicating leptomeningeal disease). Myelography generally is safe; though, it is an invasive procedure that can have side effects and has been known to cause neurological decompensation in patients with high grade blocks. Although MRI largely has replaced CT-myelography it still commonly is performed on patients that have a contraindication to MRI or who have had prior spine reconstruction with instrumentation that results in artifact (making an MRI study nondiagnostic) (Fig. 5A-B).

**TUMORS INVOLVING THE SPINE**

The epidural space is the most common compartment of the spine to be involved by metastatic disease, with the majority of epidural lesions arising from the vertebrae. When a patient presents with new or progressive spine symptoms and no epidural disease or nonneoplastic causes are identified, close inspection of the CSF spaces and spinal cord is warranted. Also, it usually is worth looking outside the spine (i.e., paraspinally) when nothing centrally fits a patient’s presentation.

**LESIONS MIMICKING METASTATIC DISEASE**

There is a subset of cancer patients who present with spine symptoms or imaging that is sometimes indeterminate for metastatic disease but which directly or indirectly reflects the sequela of treatment. Spine infections in the immunocompromised patient or even secondary malignancies occurring de novo are possible as the result of prior treatment. Radiation changes or radiation necrosis can involve the spinal cord. Nonmalignant osteoporotic type fractures of the spine are common.

**BRACHIAL AND LUMBOSACRAL PLEXUSES**

The brachial plexus is formed by the ventral rami of C5 through T1 with occasional contributions from C4 and T2. The C5 and C6 spinal nerves combine to form the superior trunk, C7 becomes the middle trunk, and the C8 and T1 nerve roots form the lower trunk. The trunks recombine to become six divisions: three anterior and three posterior. The divisions subsequently form the lateral, posterior, and medial cords which give way to the five terminal nerves (Fig. 6A-B).

The lumbosacral plexus is made up of the lumbar and sacral plexuses. The lumbar plexus is derived from the T12-L4 nerve roots with the sacral plexus derived from L4-S4 nerves. Fibers from the L4 and L5 nerve roots combine to form the lumbosacral trunk and combine with contributions from S1-S4 to form the sacral plexus. These nerves, T12-S4, divide into anterior and posterior divisions and combine to form named nerves that innervate the lower torso, pelvic girdle, and lower extremities (Fig. 7).
Imaging of the brachial and lumbosacral plexuses pose unique challenges. For the most part this is related to the complexity of the plexuses, the relative small size of the nerves that comprise the plexuses, and the relative large anatomic regions through which they course, often at an angulated spatial orientation. The basic imaging tools utilized in imaging the spine can be applied to imaging the plexus, though they need to be modified to provide the most information (i.e., lesion conspicuity), in a reasonable time frame.

Plain films have little role in the workup of a patient with a plexopathy. The soft tissue conspicuity of plain films is too low to be relevant. Myelography and CT-myelography to evaluate the plexuses seldom is needed in the cancer setting, though they can play a role in the setting of trauma if there is a question of nerve root avulsion.

As with the spine the improvements in CT has expanded the role of CT in patients with a plexopathy. Fast imaging in combination with reconstructive capabilities allow imaging of the expected course of the nerves that make up either the brachial plexus or the lumbosacral plexus. Intravenous contrast helps identify vascular structures regional to the plexuses. In the case of the lumbosacral plexus, intravenous contrast also allows the opacification of adjacent urinary structures. Oral contrast also helps identify adjacent gastrointestinal structures (i.e., the bowel). CT often can identify lesions adjacent to or compressing the plexuses but offers little soft contrast to identify the nerves themselves. CT imaging obtained in combination with a FDG-PET scan is often complimentary.

As in the spine, MRI is the primary modality for imaging of the either the brachial plexus or the lumbosacral plexus in patients with cancer. Images however are often acquired in varying plains or obliquities to best identify the plexuses. Standard T1, FSE-T2, T2 STIR, and fat suppression are commonly employed to identify abnormalities in or about the nerves. Intravenous contrast helps identify any regions of abnormal enhancement.

**ADVANCED IMAGING APPROACHES AND TECHNIQUES IN THE EVALUATION OF THE SPINE AND PLEXUSES**

Fluorine-18 (F-18) FDG-PET/CT imaging is complimentary to diagnostic MRI and CT of the spine and plexuses. In the spine F-18 FDG-PET often is requested to evaluate marrow abnormalities observed on MRI that are indeterminate for metastatic disease. A lesion that is not F-18 FDG-PET avid often is less likely to represent tumor. However, there are exceptions and follow-up imaging is needed to confirm stability of the lesion in question. As for the plexuses F-18 FDG-PET is often obtained to help distinguish between treatment change and tumor. The classic example is a patient with a brachial plexopathy who previously had radiation therapy to the region, with the MRI inclusive for posttherapy change, often showing nonspecific thickening and indistinctness of the brachial plexus. The absence of any
significant F-18 FDG-PET activity would support therapy-related change (i.e., radiation-induced fibrosis) (Fig. 8A-B).

Advanced MRI pulse sequences, some of which are fairly commonly utilized in brain imaging (e.g., diffusion weighted imaging [DWI], diffusion tensor imaging [DTI], and dynamic contrast enhanced [DCE] MRI, also known as perfusion imaging and spectroscopy) are now being applied to the spine and plexuses to evaluate lesions or abnormalities. However, applying such advanced imaging to the spine and plexuses poses significant technical challenges and should be thought of as a work in progress with the potential to provide further insight into lesions affecting the spine and plexuses.

Though overly simplified, diffusion imaging takes advantage of the fact that water molecules in some tissues diffuses equally in all directions (i.e., isotropic diffusion). In other tissues water diffusion is not equal in all directions (i.e., anisotropic diffusion). In nerves and nerve tracts water diffusion preferentially occurs along the long axis of the nerve tracts (i.e., anisotropy) while for the most part in the adjacent perineural soft tissues water diffusion occurs in all directions (i.e., isotropy). It is the differences between the water diffusion between the nerves and adjacent soft tissues that allows images to be created. In diffusion-weighted neurography axial diffusion-weighted images potentially can be processed with maximum intensity projection software to give an overview of the plexuses.

In diffusion neurography each voxel that makes up the image essentially is measuring the relative amount of water diffusion in the voxel with no regard to direction. DTI differs from simple DWI in that information regarding both the magnitude and the direction of the water diffusion—the anisotropy—are captured. The relative amount of anisotropy (i.e., fractional anisotropy [FA]) for each voxel can be displayed on a color image. From the DTI data, complex mathematical algorithms (i.e., tractography) can be employed to generate the course of the nerves. Both DWI neurography and DTI tractography can assess the integrity of nerve tracts of the spinal cord and plexuses (Fig. 9A-B).

Proton magnetic resonance spectroscopy potentially can provide metabolic information about spinal cord lesions. N-acetylaspartate (NAA) is found exclusively in neurons and axons and can assess axonal integrity. Usually a decrease in the NAA peak is suggestive of axonal dysfunction or loss. Other metabolites of interest include choline (Cho), lactate (Lac), creatine (Cr), and myo-inositol (mIns). Changes in the concentration of various metabolites may help better distinguish inflammatory processes from demyelinating lesions or tumors. Spectroscopy at this time plays little role in the evaluation of the plexuses or osseous spine lesions.

Dynamic contrast-enhanced MRI, also commonly known as MR perfusion imaging, can be performed on lesions involving the osseous spine and spinal cord. Unlike standard MR images, perfusion imaging may provide physiologic information about a lesion such as tumor vascularity and hemodynamics (Fig. 10A-C). This information may identify lesions that would benefit from preoperative embolization. Also, detecting changes in lesions vascularity potentially may be a way to assess early treatment response or progression before definitive changes are identified on standard MR imaging.
MRI should be the first imaging modality considered in the evaluation of the cancer patient presenting with symptoms referable to the spine or plexuses, with other imaging modalities playing a complimentary role. Advanced MRI techniques, while not routine, have the potential for further defining abnormalities involving the spine and plexuses, especially when clinical symptoms do not fit or are not answered by standard imaging.

**BIBLIOGRAPHY**


Mechanisms of Neurotoxicity in Cancer

Gary J. Bennett, PhD
Professor and Canada Senior Research Chair
Department of Anesthesiology
Faculty of Dentistry
The Alan Edwards Center for Research on Pain
McGill University
Montreal, Quebec, Canada

CLINICAL BACKGROUND

Chemotherapeutic agents in the taxane, platinum-complex, vinca alkaloid, and proteasome inhibitor classes all produce a chronic, distal, bilaterally symmetrical, sensory peripheral neuropathy. These drugs have different anticancer mechanisms of action, all preferentially targeted at rapidly dividing cells, yet these drugs are neurotoxic for primary afferent somatosensory neurons, which are not proliferative. The neuropathy is the dose-limiting side-effect for all of these agents, and it is the most common reason for dose reduction or discontinuation of what is otherwise life-saving therapy. The neuropathy leads to a serious decrease in the quality of life for patients under treatment, patients in remission, and for cancer survivors.6,8,9,15

Chemotherapy-evoked sensory peripheral neuropathy is accompanied by a neuropathic pain syndrome in about 20% of patients treated with standard dosages and nearly all patients receiving aggressive therapy. The syndrome is characterized by spontaneous pain, pain evoked by normally innocuous touch or cold (allodynia), and an exaggerated pain response to normally noxious mechanical stimuli (hyperalgesia).3,6,8,9 Heat hyperalgesia (an exaggerated pain response to a heat stimulus that would normally evoke pain) is either absent or minor, which is in contrast to the neuropathic pain state that follows traumatic nerve injury.7 As with other types of neuropathic pain, chemotherapy-evoked pain responds poorly or not at all to traditional analgesics in the nonsteroidal anti-inflammatory and opioid classes.

EXPERIMENTAL STUDIES

Early studies in rats and mice clearly showed chemotherapy-evoked nerve damage. But in nearly all of these studies, behavioral measures indicated that the animals had no stimulus-evoked sensation from their extremities and in some studies anatomical measures showed very extensive degeneration of axons in the peripheral nerve. Neither complete anesthesia nor pronounced axonal degeneration is a typical finding in the clinic.

More recent animal studies have used lower doses, and these studies reproduce the clinical neuropathic pain condition and do not produce axonal degeneration in the peripheral nerve. For example (Fig. 1), paclitaxel treatment (2 mg/kg, intraperitoneally [IP], four times on alternate days) produces hypersensitivity to touch (mechano-allodynia), to pin prick (mechano-hyperalgesia), and to gentle cooling (cold-allodynia). These symptoms begin...
with a delay of up to 2 weeks post-treatment, reach peak severity in about 4 weeks, and persist for 2.5 to 4 months. Very similar results are obtained with oxaliplatin (2 mg/kg, IP, 5 times daily) and bortezomib (0.2 mg/kg, IP, five times daily) (Xiao and colleagues, 2011, unpublished observations).

Animals with these neuropathic pain conditions have no degeneration in the peripheral nerve, as confirmed by quantitative electron microscopy (EM) studies. However, there is a partial (about 20%) loss of intraepidermal nerve fibers (IENFs)\(^{13,16,20,21}\); IENFs are the axonal branches that cross into the epidermis and form the afferent’s sensory terminal arbor. In paclitaxel-treated rats the degeneration has been shown to be strictly confined to the IENFs as there is no detectable degeneration below the epidermal basal lamina.\(^2\)

**Figure 2.** Chemotherapy-evoked painful peripheral neuropathy is associated with a significant increase in the incidence of swollen and vacuolated mitochondria in both A-fibers (left) and C-fibers (right). As shown here, axons generally contain a mixture of normal mitochondria (thick arrows) and swollen and vacuolated mitochondria (thin arrows). There is no effect on mitochondria in myelinating Schwann cells (not shown) or in mitochondria in the nonmyelinating Schwann cells from the C-fiber-containing Remak bundles (short thick arrow at top on right). Scale bar: 500 μm. From Xiao and Bennett.\(^{20}\)

**Figure 1.** Paclitaxel treatment (Tx) evokes mechano-allodynia (responses to 4 g VFH stimulus) and mechano-hyperalgesia (responses to 15 g VFH stimulus). Pre-paclitaxel baseline response rates are shown by the dashed lines. Note the clear delays to the onset and to the peak severity of the symptoms. Modified from Bennett, Liu, Xiao, Jin, and Siau.\(^2\) VFH = von Frey hair

**MITOCHONDRIAL ABNORMALITIES**

An unexpected observation was made during the EM study of peripheral nerve axons. Axonal mitochondria often appeared to be swollen to two to three times their normal diameters and the inner membrane was collapsed, leaving a large vacuole (Fig. 2). Subsequent quantitative EM studies of rats with paclitaxel-, oxaliplatin-, and bortezomib-evoked painful peripheral neuropathy showed that the incidence of these abnormalities was significantly increased in saphenous nerve A-fibers and C-fibers, but not in Schwann cells.\(^{11,13,20,22}\) In paclitaxel-treated rats, the abnormal mitochondria are increased in the dorsal root sensory axons but not the ventral root motor axons.\(^22\)

The integrity of the mitochondrial inner membrane is critical for establishing the hydrogen ion gradient that drives adenosine triphosphate (ATP) production via the enzyme ATP synthase. It thus appeared likely that the chemotherapeutics were causing a functional deficit in axonal mitochondria. Recent work has directly confirmed this.\(^23\) Peripheral nerve mitochondria from paclitaxel- and oxaliplatin-treated rats consume less oxygen and produce less ATP than normal, even when sampled 1 month after termination of treatment. Moreover, studies in paclitaxel-treated rats show that the mitochondrial functional deficit is present in dorsal root sensory axons but not ventral root motor axons.\(^22\)

**CONSEQUENCES OF AXONAL MITOTOXICITY**

The results described above suggest that the chemotherapeutic drugs create a persistent injury to mitochondria in sensory axons that may lead to a chronic energy deficiency. It is hypothesized that this energy deficiency is the proximate cause of all of the neuropathy’s symptoms.\(^2,11,22\)

An energy deficiency might lead to axonal depolarization because energy is need to fuel the Na⁺/K⁺ pump, which operates con-
tinually to counteract the leakage of Na+ across the membrane. A-fiber and C-fiber sensory afferents normally have no spontaneous discharge. Paclitaxel-, vincristine-, and oxaliplatin-treated rats have been found to have a clearly abnormal incidence of spontaneously discharging A-fibers and C-fibers (Fig. 3). The abnormal discharge is slow (about 1 Hz) but present in a large number of axons (10-20% of A-fibers and 20-35% of C-fibers). It is possible, but not proven, that this spontaneous discharge is responsible for the patients’ spontaneous pain and that it drives a central sensitization-like process that accounts for the allodynia and hyperalgesia.

If the mitotoxicity hypothesis is true, then the symptoms should worsen with additional mitochondrial insult. This has been confirmed (Xiao and colleagues, 2011, unpublished observations). Paclitaxel- and oxaliplatin-treated rats were given low doses of rotenone, an inhibitor of both mitochondrial respiratory complex I (oligomycin) and ATP synthase. Both poisons increased the severity of mechano-allodynia and mecano-hyperalgesia and both increased the discharge frequency of A-fibers and C-fibers with abnormal spontaneous discharge. Neither poison had any effect on the responses to mechanical stimuli in normal rats, and neither produced any motor effect (roto-rod test) in normal or chemotherapy-treated animals. Neither poison evoked any discharge in A-fibers and C-fibers in normal animals (who lack spontaneous discharge).

If severe enough, an energy deficiency would cause degeneration, and the neuronal compartment that would degenerate first would be the one with the highest energy requirement. The sensory axon’s terminal receptor arbor, its IENF, is likely to have the highest energy requirement. Mitochondria are known to concentrate in regions of high metabolic demand, and the sensory axons’ terminals are known to be packed with mitochondria. Moreover, the IENF undergoes a continuous remodeling process (alternating degeneration and regeneration) because they travel between keratinocytes and the geometry of this region is constantly changing as the skin renews itself. A partial but significant loss of about 25% in IENF density in hind paw plantar skin was found in rats with paclitaxel-, vincristine-, and oxaliplatin-, and bortezomib-evoked neuropathy (Fig. 4). The onset and progression of the IENF loss corresponds with the onset and progression of the pain symptoms.

MITOCHONDRIAL MEDICINES

If the mitotoxicity hypothesis is correct, then drugs that protect and restore mitochondrial function should inhibit the neuropathy. Acetyl-L-carnitine (ALCAR) is known to restore function to mitochondria from aged brain and to protect against various mitotoxins. ALCAR co-administered with paclitaxel and oxaliplatin has been shown to inhibit the development of the neuropathic pain state and prevents the chemotherapy-evoked deficit in mitochondrial function (Fig. 5).

Degenerative neuromuscular diseases like amyotrophic lateral sclerosis and Huntington’s disease results in the death of the lower motor neuron. Cell death is preceded by swelling and vacuolation of the neuronal mitochondria. A compound under development for such conditions, olesoxime (TRO19622), has been found...
to protect mitochondria and to be active in both preventive and treatment protocols for the neuropathies produced by vincristine, paclitaxel, and olesoxime (Fig. 6). 4,5,20,21

CONCLUSIONS

There is very strong evidence for the hypothesis that chemotherapy-evoked painful peripheral neuropathy is due to a toxic effect on the mitochondria in primary afferent sensory neurons. The reason why motor neurons are not affected is not yet understood.

Preclinical drug trials indicate that chemotherapy-evoked peripheral neuropathy is a potentially preventable and treatable condition.

ACKNOWLEDGEMENTS

Work from the author’s laboratory was supported by the National Institutes of Health (R01-NS052255), the Canada Research Chairs Program, the Canada Foundation for Infrastructure, the Louise and Alan Edwards Foundation of Montreal, the Neuropathy Association, and Trophos SA. The author is a Canada Senior Research Chair.

REFERENCES


23. Zheng H, Xiao WH, Bennett GJ. Mitotoxicity as the cause of the painful peripheral neuropathies evoked by the chemotherapeutics, paclitaxel and oxaliplatin. 2010; 13th World Congress on Pain, Abstract # PW 097.
Neuropathic Pain in Cancer

Andrea L. Cheville, MD, MSCE
Associate Professor
Department of Physical Medicine and Rehabilitation
Mayo Clinic
Rochester, Minnesota

Cancer pain incites greater dread among patients than any other dimension of the disease.1 Sadly, this fear is not unwarranted as a majority of patients with cancer, more than 90%,2 will experience pain, and among those with late stage disease it is likely to be severe.3,4 Neuropathic pain arises from pathological processes intrinsic to the nervous system, in contrast to nociceptive pain which arises from stimulation of nociceptors, the freely branching distal termini of C and A delta fibers.5 The distinction between neuropathic and nociceptive pain can have important prognostic and management implications. However, most patients with cancer experience a mixture of both, and parsing out their relative contributions to a given pain syndrome can be challenging.6 This effort is nonetheless critical. Even though treatment ultimately may be palliative, clarifying the etiologic factors driving pain can aid tremendously in the selection of effective analgesic strategies and, more broadly, in the management of patients’ cancers.

Neuropathic pain additionally warrants attention as a common harbinger of neurological compromise.7 Cancer can progress with staggering speed in the limited spaces that confine the central (CNS) and peripheral (PNS) nervous systems. Consequently, intracranial or epidural metastases have the potential to render patients plegic in a matter of hours. The warning symptoms of impending neurological catastrophe generally are present well before the onset of weakness,7 but their import may go unrecognized. A safe clinical approach among patients with cancer histories is to attribute new or worsening pain to disease progression until proven otherwise. However, even with a high level of suspicion the identification of problematic lesions may be elusive.

The stakes of accurate and timely diagnoses are frequently high, even in the more capacious surroundings of the PNS. This point is illustrated by the common plight of patients with known or suspected metastatic breast cancer who present with arm pain. Their pain often is attributed to lymphedema or musculoskeletal shoulder dysfunction without consideration of a malignant plexopathy or radiculopathy until the onset of gross weakness. Because cancer-related motor deficits are rarely reversible, a patient may have lost the use of her dominant hand or arm before temporizing treatment can be initiated. The implications for patients’ quality of life and autonomy are tremendous.

THE IMPORTANCE OF NEURODIAGNOSTICS

The contribution of neurodiagnostics (e.g., physical examination and needle electromyography [EMG]) to the management of cancer-related neuropathic pain cannot be overestimated. Earlier and more precise localization of problematic lesions may spare suffering, function, and life. Because most cancer-related pain is caused by cancer,8-10 disease-modifying therapies generally offer the most expeditious and definitive means of achieving pain relief. These include, but are not limited to, radiation, surgery, and systemic or intrathecal chemotherapy. Though highly effective, the accurate deployment of these therapies can challenge even the most seasoned clinicians. Patients’ complex presentations more often than not include a confusing mix of postradiation change, widespread metastases, and premorbid neural compromise. Imaging studies may or may not offer clarity.
MANAGEMENT OF NEUROPATHIC PAIN

Neuropathic pain that persists after disease management options have been exhausted can be effectively palliated in most patients by strategically combining analgesics. The benefits of rational polypharmacy—capitalizing on the complementarity of receptor modulators to influence nociceptive transmission—have been established for treatment for cancer-related neuropathic pain. The distinction between medications for neuropathic and nociceptive pain has blurred with the recognition that receptors with the capacity to modulate pain transmission are widely expressed in the PNS and CNS. It is increasingly unclear to what extent the nociceptive–neuropathic dichotomy has utility as a heuristic to guide analgesic selection. The assumed predominance of one pathophysiology may influence initial analgesic selection (i.e., opioid versus antiinflammatory), but thereafter choices generally are made through a hazy mix of rational receptor targeting, efforts to minimize side effects, and targeting of coexistent symptoms (e.g., insomnia, dysphoria, etc).

The serial selection of analgesics for cancer-related neuropathic pain is governed by the loose categorization scheme proposed in the World Health Organization’s analgesic ladder. The ladder suggests three broad analgesic classes—opioids, nonopioids, and adjuvants—and encourages the combined use of agents from each of these categories as appropriate. Adjuvants, depending on pain acuity and severity, generally are the initial agents of choice for neuropathic pain. Historically, adjuvants were drugs with primary indications other than analgesia (e.g., antidepressants and anticonvulsants) that serendipitously were found to have pain relieving properties. After the staggering commercial success of gabapentin, manufacturers of novel adjuvant analgesics, such as duloxetine, are increasingly seeking Food and Drug Administration approval for a pain management indication. This fact, coupled with the widespread use of adjuvants as first line and sole analgesics, have made the term somewhat dated.

Adjuvants predominantly affect activity at monoamine receptors and ion channels. A majority, particularly the more effective, are sedative with the potential to induce a host of other adverse side effects which may overlap with those of the opioids. Hence, rationale polypharmacy often becomes as much an effort to minimize dose-limiting side effects as a quest for optimized analgesia. Gabapentin, duloxetine, oxcarbazepine, and nortriptyline are all reasonable first line agents since all have established efficacy in noncancer neuropathic pain states. Few clinical trials have been conducted on cancer-specific neuropathic pain apart from chemotherapy-induced peripheral neuropathy and postoperative incisional pain.

The long-standing debate over the opioid responsiveness of neuropathic pain largely has been put to rest by several well-designed studies in conventional neuropathic pain models demonstrating unequivocal efficacy. The general tenet holds that neuropathic pain may respond less well to opioids and may require higher doses. A practice of preferentially selecting methadone to palliate neuropathic pain based on its putative N-methyl-D-aspartate (NMDA) antagonism is based purely on animal studies and has not been tested in a clinical trial. Consequently, access, cost, and convenience of dosing should dictate the choice of opioids, given the current absence of an evidence base to suggest the superiority of any particular agent for neuropathic cancer pain.

Nonsteroidal antiinflammatories and acetaminophen make up the class of nonopioids and deserve consideration in all cancer pain states since they do not cause sedation and are effective when used “as needed” (as opposed to around-the-clock). Constraints to their use arise from chemotherapy-induced toxicities (e.g., thrombocytopenia), medical comorbidities (e.g., renal insufficiency), and cancer-related hepatic and renal toxicities. Unfortunately, these issues are nontrivial and frequently, particularly in the later stages of cancer, bar the use of an otherwise effective therapy.

Topical agents similarly are free of sedation and other systemic side effects, making them an appealing treatment option when neuropathic pain is confined to a discrete area. Lidocaine-, piroxicam-, and capsaicin-impregnated patches are commercially available. Recently, a preparation of baclofen, amitriptyline, and ketamine in a pluronic lecithin organogel was found to significantly reduce pain associated with chemotherapy-induced peripheral neuropathy in a randomized, controlled trial. Case reports have suggested that relief also may be obtained with topical preparations of amitriptyline alone, but that use of stronger (e.g., 10%) preparations may limited by systemic side effects. Interventional strategies represent a valuable recourse when systemic analgesics fail. Epidural and intrathecal delivery modes offer a means to augment analgesia while reducing side effects. Surgical, radiofrequency, and cryoanalgesia and chemical neurolytic approaches may be justified when the associated loss of sensory, autonomic, or motor function is eclipsed by the mandate to alleviate suffering. The implantation of dorsal column or nerve stimulators has been considered unjustified among cancer populations.

CONCLUSION

Despite the many available therapies, cancer-related neuropathic pain often remains treatment refractory. Prevention, when possible, through early diagnosis and the timely delivery of disease-modifying therapies remains the most effective mode of control. Neurodiagnostics, too often absent from current cancer care delivery models, are a vital tool in this effort.

REFERENCES


Neuromuscular Complications of Radiation Therapy

Michael D. Stubblefield, MD  
Associate Attending Physiatrist  
Chief, Rehabilitation Medicine Service  
Department of Neurology, Rehabilitation Medicine Service  
Memorial Sloan-Kettering Cancer Center

Assistant Professor of Rehabilitation Medicine  
Department of Physical Medicine and Rehabilitation  
Weill Medical College of Cornell University  
New York, New York

INTRODUCTION

There were an estimated 13.8 million cancer survivors in 2010. This number is expected to reach 18.1 million by 2020.1 With contemporary cancer treatment strategies, about one-half of cancer patients will require radiation therapy at some point during their disease as either a curative or palliative modality.2,3 The toxicity resulting from therapeutic radiation can be a significant source of longterm neuromuscular disability. This review will discuss the pathophysiology and electrophysiological features of neuromuscular dysfunction associated with radiation therapy.

PATHOPHYSIOLOGY

The term radiation fibrosis (RF) describes the insidious pathologic fibrotic tissue sclerosis that occurs in response to radiation exposure. Radiation fibrosis syndrome (RFS), describes the clinical manifestations that result from this progressive fibrotic tissue sclerosis. In addition to the neuromuscular system, the musculoskeletal, cardiopulmonary, endocrine, gastrointestinal, genitourinary, and multiple other systems also can be adversely affected by radiation.4 Because radiotherapy often is combined with surgery and/or chemotherapy, it may be difficult to separate the neurotoxic effects of these combined modalities clinically.

The therapeutic goal of radiation therapy is to kill rapidly dividing cancer cells while sparing the more slowly dividing somatic cells. The mechanisms linking radiation to chronic vascular dysfunction and subsequent tissue sclerosis, fibrosis, and atrophy are complex and not completely understood. Free radical-mediated DNA damage and vascular endothelium injury likely are key to the process.5 In chronic radiation toxicity, microvascular injury and an abnormal feedback loop created by cytokines and other inflammatory mediators may play a pivotal role in the self-perpetuating nature of the radiation injury. This results in abnormal accumulation of fibrin in the intravascular, perivascular, and extravascular compartments.5 It is this abnormal accumulation of fibrin and subsequent progressive tissue fibrosis and sclerosis that likely underly RF and result in the RFS.

Three histopathological phases of RF have been described. The prefibrotic phase is characterized by chronic inflammation and, likely, endothelial dysfunction. The organized fibrotic phase demonstrates patchy areas of active fibrosis containing a high density of myofibroblasts in an unorganized matrix adjacent to poorly cellularized fibrotic areas of senescent fibrocytes in a dense sclerotic matrix. Features of the late fibroatrophy phase are retractile fibrosis and gradual loss of parenchymal cells.4

RF can affect any tissue type. Commonly affected tissues include skin, muscle, ligament, tendon, nerve, heart, lung, gastrointestinal, or genitourinary tract and bone.7,10 Radiation effects can be acute (occurring during or immediately after treatment), early-delayed (up to 3 months after completion of treatment), or late-delayed (occurring more than 3 months following completion of treatment).11 RF can present in the first several months following treatment or many years later. When it does manifest it may progress rapidly over weeks or months or insidiously over decades. The rule is one of progression as the underlying DNA damage and pathophysiological changes that perpetuate the tissue damage are not reversible.12,13
RADIATION DELIVERY

A prerequisite for understanding RFS is a basic understanding of how therapeutic radiation is delivered. The two basic strategies of radiation delivery are external beam radiation where radiation is delivered from outside the body and brachytherapy where radiation is delivered from within the body. Dose-sculpting strategies have been developed that allow three-dimensional targeting of radiation to tumor with relative sparing of normal surrounding tissues. These techniques include intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT). IMRT utilizes multileaf collimators to subdivide radiation beams into beamlets and aim them at the tumor from multiple directions. This allows the beam to be conformed tightly to the three-dimensional shape of the tumor.

In IGRT imaging such as computed tomography is incorporated during the treatment process. This allows for compensation of tumor movement during or between treatment sessions as would occur with tumor perfusion, respiration, shrinkage from the last radiation session, or other factors. IGRT allows for even tighter control of radiation dosing than IMRT and has drastically changed treatment strategies for what were previously considered radioresistant tumors such as melanoma and renal cell carcinoma. These tumors can now be targeted with the expectation of excellent clinical results even when they are located only a few millimeters away from radiosensitive structures such as the spinal cord. Although conformal radiotherapeutic techniques such as IGRT and IMRT have revolutionized many aspects of cancer treatment, there is a potential neuromuscular downside of being able to focus such high doses of radiation into a single fraction (or few fractions) as will be discussed below.

A major determinant of the potential severity of RFS is the size of the field encompassed by radiation. The radiation fields traditionally used to treat Hodgkin lymphoma (HL) and other lymphomas can be extensive (Fig. 1). The commonly used fields are the mantle field (MF) which includes all lymph nodes in the neck, chest (exclusive of the lungs which were shielded), and axilla, and the inverted-Y field, which includes the periaortic and ilioinguinal lymph nodes. A combination of MF and inverted-Y radiation is known as total nodal radiation. The neuromuscular impact of radiation to these fields can be devastating and will be discussed in detail below.

Patients radiated for head and neck cancer (HNC) are also at risk for RFS. Contemporary doses to the primary tumor may be as high as 7,000 cGy. Conformal radiation techniques such as IMRT have shown significant benefits in improving local control and decreasing both acute and late toxicities. Multiple neuromuscular structures, however, including the cervical nerve roots, brachial plexus, local nerves, and muscles are encompassed by the radiation field and are at risk for damage.

NEUROMUSCULAR COMPLICATIONS OF RADIATION THERAPY

Nerve

The neuromuscular complications of radiation on nerve likely are a result of both direct effects on neural structures and indirect effects on their supporting tissues. The same progressive fibrotic sclerosis that affects other tissues also affects the brain, spinal cord, nerve root, plexus, as well as all components of the peripheral nerve (motor, sensory, autonomic), and muscle. Understanding the effects of RF on neural tissue is important to understanding the clinical neuromuscular manifestations of RFS. The structures affected will depend on the type of radiation given, dose, time since radiation, number of fractions (single or oligo often being more toxic than multiple), size and location of the radiation field, and, critically, the neural structures encompassed by the radiation field.

Dysfunction of the peripheral nervous system (PNS) results from either external compressive fibrosis of soft tissues or ischemia due to fibrosis and subsequent compromise of the vas vasorum or a combination of both processes. Clinically, pain, sensory loss, and weakness commonly are seen as a result of PNS dysfunction at any level in RFS. Autonomic dysfunction also is observed in RFS and manifests clinically as orthostatic hypotension, bowel and bladder change, sexual dysfunction, and other abnormalities. Neuropathic pain is common in RFS and results from damage to neural structures such as the nerve roots, plexus, and/or peripheral
nerves involved within the radiation field. The genesis of neuropathic pain is complex and generally involves both the central and peripheral nervous systems. The pathogenesis of neuropathic pain in RFS likely involves the generation of ectopic activity in radiation-damaged components of the PNS. Radiation-induced ectopic activity potentially can develop in any affected neural structure including the thalamus, ascending spinothalamic tracts, nerve roots, plexus, and peripheral nerves. The etiology of the ectopic signal can be compressive and/or ischemic with subsequent demyelination and/or axonal loss. Pre-existing medical or degenerative disorders such as diabetes or spinal stenosis also may contribute significantly to neuropathic pain in RFS patients by leaving them predisposed to the effects of radiation.

Weakness, as with neuropathic pain and sensory loss, can be caused by damage to any level of the neuromuscular axis including the brain, spinal cord, peripheral nerve, and muscle. Damage to the nerve roots causes weakness in a myotomal pattern. Multiple nerve roots are often involved depending on the size and scope of the radiation field. This is of particular clinical significance for HNC and HL survivors. In HNC patients, the upper cervical nerve roots (C5 and C6) are often encompassed by the radiation field used to treat cervical lymph nodes. All cervical nerve roots are encompassed by the MF and the cauda equina by the para-aortic, inverted-Y, or total nodal fields.

Radiation-induced plexopathy can affect the cervical, brachial, and lumbosacral plexus resulting in significant pain and/or weakness. Differentiating radiation-induced plexopathy from neoplastic plexopathy represents a diagnostic challenge that is now somewhat easier with improved imaging techniques. The upper brachial plexus appears more susceptible to radiation injury clinically. This may be due to its apical location in the neck and the long course traversed by its fibers relative to the middle and lower trunk. These anatomical differences would place more of the upper trunk of the plexus within the radiation field of many HNC ports. The pyramidal shape of the thorax and the clavicle have been postulated to provide some protection for the middle and lower plexus relative to the upper plexus, but the clinical validity of this phenomenon is unclear and has not been proven.

Individual nerves are as susceptible to the effects of radiation as the nerve roots and plexus. Dysfunction generally is obvious when a large named nerve such as the sciatic nerve is squarely in the radiation field. It may be less so when a lesser nerve or unnamed nerve is involved. For instance, in some HL survivors treated with MF radiation, the nerves innervating the rotator cuff muscles, such as the dorsal scapular nerve to the rhomboids and the suprascapular nerve to the supraspinatus and infraspinatus muscles, are commonly affected. This can contribute significantly to shoulder atrophy, pain and dysfunction. Similarly, the bilateral phrenic nerves may be compromised, contributing to pulmonary insufficiency.

Muscle

Radiation damage to muscle can cause a focal myopathy associated with nemaline rods in HL survivors. Clinically, these myopathic muscles are prone to painful spasms. Several pathologic mechanisms likely underlie these painful spasms including the myopathy itself, weakness and fatigability of affected muscle, and ectopic activity in the motor nerve innervating the muscle. Ectopic activity in the innervating motor nerve would result in volleys of neural activity being transmitted to and across the neuromuscular junction resulting in a muscle spasm. Myokymia is one such form of spontaneously generated ectopic activity. Though usually thought to be generated by ephaptic cross talk between demyelinated axons, it has also been reported in axonal disorders. The spasm generally does not result in a sustained contraction clinically but rather is perceived as vague tightness by the patient. Persistent spasm of key muscles (i.e., sternocleidomastoid and scalene) in HNC patients coupled with sclerosis and foreshortening of tendons and ligaments of the neck likely contributes to clinical disorders such as radiation-induced cervical dystonia and, ultimately, fixed contracture of the neck (Fig. 2).

Myelo-radiculo-plexo-neuro-myopathy

As discussed earlier, the clinical manifestations experienced and exhibited by a patient treated with radiation therapy will depend on many factors. Among the most important of these are the size of the radiation field and the neuromuscular structures it encompasses. For HL patients, these fields can be extensive and involve nearly the entire spinal cord, most nerve roots, the brachial and lumbosacral plexus, multiple named and unnamed peripheral nerves, and large volumes of muscle, including the rotator cuff muscles and the paraspinal muscles. Due to the insidious nature of RF and the progressive nature of RFS, the clinical ramifications of a given patient’s radiation treatment becomes more evident as time progresses.

In HL survivors it is not uncommon to see clinical evidence of myelopathy (spasticity, paraplegia, quadriplegia, detrusor-sphincter dysynergia), radiculopathy (radicular pain, myotomal

Figure 2. Radiation induced cervical dystonia in a head and neck cancer patient treated with surgery and high-dose radiation. The sternocleidomastoid, scalene, and other neck muscles are painful to palpation, fibrotic, and prone to spasm. The surrounding connective tissues including the skin are also fibrotic, sclerotic, and poorly mobile. The clinical result is markedly diminished neck mobility and pain.
weakness, electrophysiological evidence, leptomeningeal enhancement on magnetic resonance imaging [MRI]),29 plexopathy (clinical upper or lower trunk involvement, flail atrophic arm, electrophysiological evidence, plexus enhancement on MRI),23 mononeuropathy (spinal accessory, dorsal scapular, phrenic nerves),25 and myopathy (myopathic motor units, early recruitment in the radiation field).8 The author has coined the term “myelo-radiculo-plexo-neuro-myopathy” to describe, in anatomical sequence, the structures affected by RF and responsible for RFS in HL and other patients treated with such extensive radiation fields (Fig. 3).

It should be noted that there is tremendous variability in how individual patients are affected and not all structures will be affected equally even given seemingly identical treatments in terms of field, dose, body habitus, and time since treatment. Some patients may present with severe myelopathy with little PNS dysfunction. Other patients may have severe plexopathy with relative preservation of other structures (Fig. 4).

The most common clinical syndrome encountered in HL survivors is neck extensor weakness, which likely is a combination of dysfunction of the cervical nerve roots, potentially cervical plexus, and, most significantly, cervical and upper thoracic paraspinal muscles (Fig. 5). Similarly, shoulder girdle weakness and pain is encountered with great frequency in HL survivors likely due to involvement of the upper cervical (C5 and C6) nerve roots, upper brachial plexus, and rotator cuff muscles.

HNC patients treated with conventional conformal radiation are spared toxicity to the spinal cord. Their cervical nerve roots, plexus, and local muscles, however, receive high doses of

Figure 3. Typical findings in a 51-year-old Hodgkin lymphoma survivor treated with mantle and peri-aortic radiation 29 years previously. Note the severe atrophy of the trapezius, cervicothoracic paraspinal, rhomboid, and deltoid muscles (A). The pectoral muscles which were shielded with the lungs are relatively preserved (B). The patient has severe neuromuscular and musculoskeletal dysfunction including polyradiculopathy characterized by nodular enhancement of his cauda equina on gadolinium enhanced T1 weighted magnetic resonance imaging (C, white arrow), and clinically by plexopathy, mononeuropathies, and myopathy in the radiation field. No significant evidence for myelopathy was present at the time of the last examination. This patient has excellent posture for a Hodgkin lymphoma survivor which represents extensive and effective rehabilitation efforts. Despite these efforts, he still has significant gait dysfunction due to lower extremity weakness. He saw multiple neurologists prior to being diagnosed with radiation fibrosis syndrome and was at one point given a provisional diagnosis of chronic idiopathic demyelinating polyradiculoneuropathy. A nerve biopsy however demonstrated an axonal process.

Figure 4. T1-weighted magnetic resonance imaging depicting radiation changes in the right brachial plexus (white arrow) of a 52-year-old Hodgkin lymphoma survivor 37 years following mantle field radiation. While her entire right plexus was involved clinically, the most severe findings were in the distribution of the lower plexus. The left plexus was not significantly involved clinically, demonstrating the patchy nature of dysfunction in this patient.
Neck extensor weakness in a 77-year-old male Hodgkin lymphoma survivor treated with mantle field radiation 26 years previously. The severity of his symptoms reflects not only the radiation treatment but also the predisposing effects of advanced degenerative disease of the spine. Note the marked atrophy of the cervicothoracic and rotator cuff muscles.

Radiation, placing them at risk for RFS that can occur much earlier than what is observed in HL survivors. Neck extensor weakness does occur, but because the thoracic paraspinal muscles are outside the radiation field used to treat the cervical lymph nodes, it is generally less severe. Shoulder dysfunction, however, can be a source of great disability in HNC patients.

Conformal Radiation and Mononeuropathies

Dose sculpting techniques promise improved tumor control with reduced toxicity. While this may be the outcome for the vast majority of cases, the author has encountered multiple instances of severe neuromuscular toxicity as a direct result of single fraction or, less commonly, hypofractionated radiation. Toxicities observed include painful mononeuropathies of the sciatric or femoral nerve 12 to 24 months following single fraction IGRT to the proximal femur or pelvis (i.e., lesser trochanter, acetabulum), radiculopathy (L3) and radiculo-plexopathy (C7 paravertebral).

CONCLUSION

Radiation toxicity is a potential source of significant neuromuscular dysfunction and disability in cancer survivors. The manifestations of radiation can be subtle or overt depending on a variety of factors including the size and scope of the radiation field, the structures contained within it, the dose of radiation given, and the amount of time elapsed since radiation. Given the rapidly expanding number of patients who will be joining the ranks of cancer survivors in coming years, neuromuscular specialists should be aware of the toxicity associated with radiation. This will allow a meaningful incorporation of radiation toxicity into the differential diagnosis of neuromuscular dysfunction when assessing such patients.

REFERENCES

Plenary: Neuromuscular Complications of Cancer and Its Treatment

CME Questions

1. A 77-year-old male with new onset fatigable ptosis and diplopia was found to have elevated levels of autoantibodies against muscle acetylcholine receptor (AChR), as well as AChR modulating antibodies (90%) and striational antibodies (1:7,680). His exam shows weakness only in the ocular muscles. What is the likelihood that this patient has thymoma (i.e. paraneoplastic myasthenia gravis)?
   A. No possibility. Thymoma is never seen in patients with ocular myasthenia.
   B. Unlikely. Thymoma is not usually associated with ocular myasthenia, but a chest CT is warranted to make sure.
   C. Likely. The risk of thymoma is high in patients with late onset myasthenia gravis
   D. Very likely. The high levels of modulating and striational antibodies are highly predictive of thymoma in this case.

2. What is the most common paraneoplastic syndrome encountered in patients with small-cell lung carcinoma?
   A. Axonal peripheral sensory and motor neuropathy.
   B. Pure sensory neuropathy (or sensory neuronopathy).
   C. Dermatomyositis.
   D. Lambert-Eaton myasthenic syndrome.

3. When a paraneoplastic syndrome affects the autonomic nervous system, which of the following is the most common presentation?
   A. Orthostatic hypotension.
   B. Dry mouth and dry eyes (mimicking Sjogren syndrome).
   C. Gastrointestinal dysmotility (nausea, vomiting and constipation).
   D. Urinary incontinence.

4. A 62-year-old female with a 30-year history of smoking presents with weight loss, anosmia, loss of balance, and tingling and pain in the feet. Exam shows loss of vibration and joint position sensation in the toes and ankles. Tendon reflexes are absent in the legs. She has a wide-based unsteady gait, and her balance worsens when she closes her eyes. Examination of cerebrospinal fluid is normal. A complete assessment for all known paraneoplastic autoantibodies is negative (both serum and CSF). Contrast-enhanced computed tomography of the chest, abdomen, and pelvis is unremarkable. What is next best course of action?
   A. Reassure the patient that she is unlikely to have cancer because the antibody tests are negative and the computerized tomography (CT) scan is normal.
   B. Consider fluorodeoxyglucose-positive emission tomography (PET) scan of the body to look for occult malignancy and/or repeat body CT scans in 3 months because the likelihood of cancer is high
   C. Repeat paraneoplastic antibody studies in case there was a laboratory error.
   D. Initiate treatment with standard chemotherapy for small-cell lung cancer.

5. Which statement summarizes the clinical significance and difference between ion channel autoantibodies and paraneoplastic nuclear and cytoplasmic antibodies?
   A. The presence of either type of antibody is highly predictive of cancer, but only the ion channel antibodies are a direct cause of disease.
   B. Paraneoplastic nuclear and cytoplasmic antibodies are highly predictive of cancer. Ion channel antibodies correlate well with particular disease syndromes but do not strongly predict the presence of malignancy.
   C. Disorders associated with nuclear and cytoplasmic antibodies generally show clinical improvement after plasma exchange and immunosuppression, while those associated with ion channel antibodies have a poor prognosis.
   D. Ion channel antibodies cause neuromuscular disorders, while nuclear and cytoplasmic antibodies cause syndromes of the central nervous system.
6. Neoplastic brachial plexopathy most commonly occurs in patients:
   A. Who are at initial presentation of their cancer.
   B. Who also have lumbosacral plexopathy.
   C. With active widespread metastatic disease.
   D. With concomitant vertebral involvement.

7. Neoplastic invasion of the lumbosacral trunk over the sacral ala produces:
   A. Weakness of foot plantar flexion and incontinence.
   B. Weakness of knee extension and a “hot dry foot”.
   C. Weakness of the pelvic floor muscles and incontinence.
   D. Weakness of foot dorsiflexion and plantar inversion.

8. Other than neoplastic involvement, the most common differential diagnostic consideration for plexopathy in treated cancer patients is:
   A. Paraneoplastic plexopathy.
   B. Radiation plexopathy.
   C. Injury from intra-arterial chemotherapy.
   D. Vasculitic plexopathy.

9. A lung cancer patient with right upper extremity C8-T1 distribution pain, Horner’s syndrome, and electromyographic evidence of asymmetrical bilateral proximal and distal lower extremity active denervation, is likely to have metastasis to the:
   A. Bifrontal region and a C7 herniated disc.
   B. T1 vertebra and epidural cord compression.
   C. T1 vertebra, brachial plexus, and paraneoplastic neuropathy.
   D. Brachial plexus and leptomeninges.

10. Three of the most helpful tests that help distinguish neoplastic from radiation-induced plexopathy are:
    A. Magnetic resonance imaging (MRI), PET scan, and needle electromyography (EMG).
    B. MRI, serum tumor markers, and EMG.
    C. Computerized tomography, PET scan, and EMG.
    D. MRI neurography, serum tumor markers, and EMG.

11. In the cancer patient with symptoms thought to be related to the spine or plexuses, the imaging study of choice is:
    A. PET-CT.
    B. Plain Films.
    C. MRI.
    D. Myelography.

12. The most common anatomic compartment of the spine to be involved by metastatic disease is the _____ space.
    A. Intradural.
    B. Epidural.
    C. Leptomeningeal.
    D. Intramedullary.

13. On MRI bone metastasis are most typically:
    A. Hypointense (dark) on T1 weighted images and hyperintense (bright) on T2 weighted images.
    B. Hyperintense (bright) on T1 weighted images and hypointense (dark) on T2 weighted images.
    C. Do not enhance.
    D. Remain hyperintense (bright) on both the T1 and T2 weighted images.

14. Which of the following is true?
    A. Myelography is the study of choice in the evaluation of metastatic disease to the spine.
    B. Is a useful alternative to image the spine when a patient is unable to have a MRI or when prior spine surgery degrades the MRI.
    C. Is a noninvasive procedure.
    D. Is also known as a contrast enhanced CT.

15. The diffusion of water molecules in all directions is known as:
    A. Anisotropic diffusion.
    B. Isotropic diffusion.
    C. Diffusion tensor imaging.
    D. Diffusion tractography.

16. In experimental chemotherapy-evoked painful peripheral neuropathy, the animals have allodynia and hyperalgesia, and:
    A. Degeneration of dorsal root ganglion cells.
    B. Extensive degeneration of axons in peripheral nerve.
    C. Degeneration of spinothalamic tract axons.
    D. Partial degeneration of sensory axon terminal arbors.

17. Mitochondrial swelling and vacuolation suggest impaired energy production because:
    A. An intact inner mitochondrial membrane is required to maintain the hydrogen ion (proton) gradient.
    B. Swelling and vacuolation dilute the mitochondrial matrix, thus reducing substrate availability.
    C. Swelling and vacuolation rupture the mitochondrial outer membrane, killing the mitochondria.
    D. Vacuoles produced by swelling are an acidic compartment that poisons respiration.

18. Chemotherapy-evoked painful peripheral neuropathy is associated with:
    A. A high frequency spontaneous discharge in A-fibers and C-fibers.
    B. A high frequency spontaneous discharge in C-fibers only.
    C. A low frequency spontaneous discharge in A-fibers and C-fibers.
    D. A low frequency spontaneous discharge in C-fibers only.

19. Symptoms that first appear weeks after terminating chemotherapy are:
    A. Unlikely to be due to the chemotherapeutic drug.
    B. Indicative of chemotherapy-evoked kidney damage.
    C. Characteristic only of chemotherapeutics in the taxane class.
    D. A common occurrence in all chemotherapy-evoked neuropathies.
20. The difference between intensity modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT) is that:
   A. IMRT allows the dose of radiation to modulate by varying the current to the generator.
   B. IMRT never incorporates imaging into the treatment planning.
   C. IGRT incorporates imaging during treatment.
   D. IGRT is not a conformal radiation technique.

21. The primary source of nerve and muscle pathology in radiation fibrosis syndrome is thought to be mediated by dysfunction of the:
   A. Endotheliocytes.
   B. Lymphatics.
   C. Histiocytes.
   D. Fibroblasts.

22. The mantle field radiation traditionally used to treat Hodgkin lymphoma includes all lymph nodes in the:
   A. Neck, chest, and axilla.
   B. Neck, chest, axilla, and abdomen.
   C. Neck, chest, axilla, abdomen, and pelvis.
   D. Neck, chest, axilla, abdomen, pelvis, and groin.

23. Factors potentially contributing to cervicothoracic weakness, atrophy, and pain in a Hodgkin lymphoma survivor 30 years following treatment with mantle field radiation include:
   A. Radiculopathy.
   B. Plexopathy.
   C. Mononeuropathy.
   D. Myopathy.
   E. All of the above.

24. Factors potentially contributing to lower extremity weakness and gait dysfunction in a Hodgkin lymphoma survivor 30 years following treatment with total nodal radiation include:
   A. Myelopathy.
   B. Radiculopathy.
   C. Plexopathy.
   D. Mononeuropathy.
   E. All of the above.