

Paraneoplastic Syndromes and the Nervous System

Michael Rubin, MD, FRCP(C)

Commentary on “Neuromuscular Complications of Cancer Diagnosis and Treatment” by Mohamed Falah, MD, David Schiff, MD, and Ted M. Burns, MD (page 271).

Neurologic complications of malignancy affect either the central or peripheral nervous system, including the neuromuscular junction and striated muscle. These complications occur in up to 20% of cancer patients and result from the direct space-occupying effects of cancer, from malnutrition, or from iatrogenic effects of chemo- or radiotherapy. Most intriguing, however, are the paraneoplastic syndromes, immune-mediated remote effects of cancer, which despite their rarity (except for myasthenia gravis), capture attention far beyond their impact.

Diagnosis of a paraneoplastic syndrome may be difficult, particularly since most patients present before they are known to have cancer. Certain clues are helpful. Symptoms often develop abruptly and evolve rapidly over days and weeks, rendering the patient disabled—if not bedridden—before stabilizing within weeks to months.¹ Cerebrospinal fluid (CSF) is frequently abnormal if the syndrome affects the central nervous system (CNS), demonstrating lymphocytosis, positive oligoclonal banding, and immunoglobulin G elevation, with titers of paraneoplastic antibodies, if present, higher in CSF than in serum. Some patients have antibodies in serum but not in CSF, and therefore antibody studies of both are recommended. Persons without paraneoplastic disease occasionally may have these antibodies but when encountered in someone with an undiagnosed neurologic disease, paraneoplasia should be suspected. If a patient is suspected of having

a paraneoplastic syndrome but is antibody-negative, investigation should focus on other serologic markers of cancer, including carcinoembryonic antigen, cancer antigen (CA)-125, CA-15-3, and prostate specific antigen.

Aggressive search for the suspected cancer should include serum immunoelectrophoresis; skeletal survey; computerized tomography of the chest, abdomen, and pelvis; testicular ultrasonography; magnetic resonance imaging; and positron emission tomography (PET) scanning with the glucose analog 2-¹⁸F-fluoro-2-deoxy-D-glucose. The best treatment, though not guaranteed, is discovery and removal of the occult tumor. Finding a cancer not usually associated with a paraneoplastic antibody should prompt the search for a second cancer, particularly if the tumor found does not express the target antigen of the paraneoplastic antibody.²

What is the mechanism of paraneoplasia? Paraneoplastic syndromes may be the ill-fated immune-mediated by-product of the body's attempt to destroy or contain the cancer. Certain cancers share protein antigens with CNS tissue. When these cancers develop, the immune system may recognize them as foreign and raise an antibody response, which may injure CNS tissue while trying to eliminate the tumor.

Several lines of evidence support this autoimmune hypothesis. Antibodies are present in high titers in the serum of patients with paraneoplastic syndromes, and they react exclusively with antigens in the tumor and nervous tissue. Positive antibody titers in the CSF indicate that they are synthesized within the CNS; these antibody titers have also been reported intraneuronally, though their presence here remains the subject of debate. Patients with paraneoplastic syndromes have long been recognized to experience slower tumor growth than their nonparaneoplastic counterparts, a fact that has now been documented both in the clinic and in the laboratory.^{3,4} Paraneoplastic antibodies may be responsible for this

Dr. Rubin is an Attending Neurologist and Director of the Neuromuscular Service, New York Presbyterian Hospital-Cornell Medical Center, and Professor of Clinical Neurology, Joan and Sanford I. Weill Medical College, Cornell University, New York, New York.

Correspondence to: Michael Rubin, MD, Neuromuscular Service, 520 East 70th Street, STARR-607, New York, NY 10021; telephone: (212) 746-2320; fax: (212) 746-5509; e-mail: mprubin@med.cornell.edu

J Support Oncol 2005;3:287-288

© 2005 Elsevier Inc. All rights reserved.

phenomenon. Lastly, blood, CSF, and brain tissue of paraneoplastic patients contain T cells that are antigen-specific, suggesting that they play a role in etiopathogenesis.

Common Problems

In this issue, Falah et al comprehensively review the diagnosis of these and other neuromuscular complications of cancer. A few additional points underscore the importance of this timely review. Neuromuscular disease in the cancer population is more common than appreciated. Abnormalities have been found on electromyographic (EMG) examination, though not on nerve conduction studies, in up to 40% of patients with lung cancer, even in the absence of symptoms.⁵ Electrodiagnostic studies demonstrate fasciculation potentials and myokymic discharges in 60%–70% of patients with radiation-induced nerve injury, a sensitive and characteristic finding, though one that remains nonspecific. Chronic changes in the form of large amplitude, long-duration polyphasic motor unit potentials on EMG are seen in most patients with either radiation-induced or carcinomatous plexopathy. Electrophysiologic studies thus have a central role in the diagnosis of these disorders.

Treatment of the neuromuscular complications is also discussed by Falah et al. Not to be overlooked is the fact that mus-

cle wasting, or cachexia, is present in 50% of cancer patients, is directly responsible for 20% of cancer deaths, and will have to be countered if morbidity statistics are going to change.⁶ Although long considered a late complication, muscle wasting is frequently evident at the time of diagnosis, including in 80% of patients with upper gastrointestinal tract malignancies and in 60% of patients with lung cancers.

Hypercatabolism of actin and myosin is the key feature of this muscle loss, and cytokine-dependent calpain activation may be central to the process. Adenosine triphosphate-dependent ubiquitin proteolysis and ubiquitin messenger RNA overexpression, even prior to significant weight loss in cancer patients, suggest that the mechanisms of cancer cachexia are operative early, emphasizing the need for early intervention if this process is to be halted or slowed. Attenuating muscle protein catabolism and stimulating anabolism remain challenging prospects in countering cachexia but at present remain at the experimental level. These approaches include cytokine or proteasome inhibition on the one hand and anabolic androgenic steroids on the other. Controlled clinical trials are needed to evaluate these promising avenues of research, both for efficacy and safety. Meanwhile, aggressive treatment of the underlying cancer is the best we have to offer.

References

1. Posner JB. Immunology of paraneoplastic syndromes. *Ann N Y Acad Sci* 2003;998:178–186.
2. Rosenfeld MR, Dalmau J. Current therapies for paraneoplastic neurologic syndromes. *Curr Treat Options Neurol* 2003;5:69–77.
3. Graus F, Dalmau J, Reñé R, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. *J Clin Oncol* 1997;15:2866–2872.
4. Carpentier AF, Rosenfeld MR, Delattre JY, et al. DNA vaccination with HuD inhibits growth of a neuroblastoma in mice. *Clin Cancer Res* 1998;4:2819–2824.
5. Trojaborg W, Frantzen E, Andersen I. Peripheral neuropathy and myopathy associated with carcinoma of the lung. *Brain* 1969;92:71–82.
6. Muscaritoli M, Bossola M, Bellantone R, Fanelli FR. Therapy of muscle wasting in cancer: what is the future? *Curr Opin Clin Nutr Metab Care* 2004;7:459–466.