Paraneoplastic Disorders in Thymoma Patients

Amelia Evoli, MD, and Eric Lancaster, MD, PhD†*

Abstract: Thymic malignancy is often associated with paraneoplastic neurological diseases (PNDs) and recognition of these disorders is important for physicians who treat these patients. The most common thymoma-associated PNDs are myasthenia gravis (MG), acquired neuromyotonia (Isaacs' syndrome), encephalitis, Morvan's syndrome, and myositis. Diagnosis of these disorders is complex but often aided by testing for specific autoantibodies, including those to the acetylcholine receptor for MG and to contactin-associated protein-like 2, protein of the voltage-gated potassium channel complex, in patients with acquired neuromyotonia, Morvan's syndrome, or encephalitis. Patients who manifest these disorders should be screened for thymoma at diagnosis, and worsening of these PNDs may be associated with recurrent thymoma. These disorders can cause profound disability but usually respond to immunotherapy, and often improve with thymoma treatment. Close cooperation among a team of specialists is required to take proper care of these patients.

Key Words: Paraneoplastic, Thymoma, Thymic tumor, Neuromyotonia, Myasthenia gravis, Antibodies, VGKC antibodies, Encephalitis, Isaacs' syndrome, Morvan's syndrome, Myositis, Lambert Eaton Syndrome.

(*J Thorac Oncol*. 2014;9: S143–S147)

Patients with cancer may rarely be affected by unusual neurological symptoms associated with their tumors, but caused neither by direct nervous system invasion by the tumor nor by any obvious metabolic or toxic mechanism.[1] These paraneoplastic disorders may affect many organ systems, but many of the most complex and serious manifestations result from the involvement of the nervous system. Although several potential causes for paraneoplastic disorders were proposed, including "bad humors" secreted by tumors, autoantibody markers have been detected and most of these disorders have an established autoimmune basis.[2] The thymus is a central organ for the development of the immune system, particularly for the selection of T cells with appropriate self-tolerance.[3,4] It is therefore unsurprising that patients with thymic epithelial cell tumors may develop paraneoplastic neurological diseases (PNDs) at any point in their disease course. Although multiple systemic autoimmune disorders associated with thymoma have been described, this review focuses on the neurological PND most likely to be found in these patients. The symptoms, diagnostic tests, specific autoantibody markers, and treatments of the paraneoplastic disorders associated with thymoma are summarized in Table 1, and covered in detail below.

*Department of Neurology, Catholic University, Roma, Italy; and †Department of Neurology, The University of Pennsylvania, Philadelphia, PA.

Disclosure: The authors declare no conflict of interest.

E.L. is supported by an award from the Dana Foundation and K08 NS075142.

Address for correspondence: Eric Lancaster, MD, PhD, The University of Pennsylvania, 3400 Spruce St., 3 W. Gates Building Philadelphia, PA 19104. E-mail: eric.lancaster@uphs.upenn.edu

ISSN: 1556-0864/14/0909-S143

PARANEOPLASTIC NEUROLOGICAL DISORDERS ASSOCIATED WITH THYMIC MALIGNANCY

Disorders of Neuromuscular Transmission

Myasthenia gravis (MG) is by far the most common of these disorders, as 15% to 20% of MG patients have a thymoma, while 24.5% to 40% of thymoma patients develop MG.[3,5] The clinical hallmark of MG is fatigable muscle weakness. Although symptom extension varies broadly, some muscle groups are more commonly involved than others, with a typical weakness pattern in most cases. MG should be suspected in patients presenting with asymmetric eyelid ptosis and diplopia, often associated with dysarthria and dysphagia ("bulbar" symptoms), facial and neck weakness. Limb involvement is usually prevalent in proximal muscles; respiratory weakness may result in crisis or death. Several antibodies (Abs) have been described in MG. Pathogenic Abs bind to extracellular determinants of postsynaptic membrane proteins, and cause morphological and functional alterations that interfere with neuromuscular transmission (NMT). In 85% of patients, such Abs target the acetylcholine receptor (AChR-Abs); in 5% of cases, Abs to the muscle-specific tyrosine kinase (MuSK) are detected, while in a proportion of AChR/MuSK-negative patients, Abs against the low-density lipoprotein-related protein 4, which is the MuSK co-receptor for agrin, have been described.[6] In patients with thymoma, MG is nearly invariably associated with AChR-Abs, which can also occur in rare thymoma cases without neurological symptoms. Abs against the muscle giant protein titin, formerly identified as "striational" muscle Abs, and anti-ryanodine receptor are found in a high proportion of thymoma-MG cases and, with a lower frequency, in late-onset MG. Although of uncertain pathogenicity (as directed against intracellular antigens), these Abs are markers of thymoma, at least in patients younger than 50 years at MG onset.[6]

Diagnosis is confirmed by Ab testing and electromyography studies showing a postsynaptic NMT defect, including a significant decrement in the compound muscle action potential (CMAP) on low-frequency repetitive nerve stimulation (RNS) or increased jitter on single-fiber EMG[7]; a clear-cut clinical response to cholinesterase inhibitors (ChE-Is) further supports the diagnosis. MG treatment is tailored on disease

TABLE 1. Paraneoplastic Syndromes Associated with Thymoma, Relevant Antibodies, Diagnostic Tests, and Treatments

Paraneoplastic Condition	Findings	Autoantibodies	Other Diagnostics	Treatments
MG	Fatigable weakness with variable extension (from ocular to generalized)	AchR-MuSK (very rare)	EMG	Steroids, pyridostigmine, immunosuppressants, IVIG, plasmapheresis
Lambert Eaton syndrome (very rare)	Fatigable weakness, autonomic symptoms	VGCC	EMG	3,4-diaminopyridine Steroids, IVIG, plasmapheresis
Myositis	Muscle pain, weakness elevated creatine kinase		EMG	Steroids
Acquired neuromyotonia	Diffuse fasciculations, cramps, hyperhidrosis	Caspr2 (and potentially other members of the VGKC complex)	EMG/NCS	Sodium channel blockers (phenytoin), IVIG, plasmapheresis, steroids
Encephalitis	Memory impairment, behavioral changes, hallucinations, seizures, altered level of consciousness	Caspr2 (most common in thymoma patients) AMPAR CV2/CMRP5 Others unknown	CSF analysis, brain MRI, EEG	Steroids, IVIG, rituximab, cyclophosphamide
Morvan's syndrome	Neuromyotonia and encephalitis, often with sleep disorder	Caspr2 (and potentially other members of the VGKC complex)	CSF analysis, brain MRI, EEG, EMG	Steroids, IVIG, rituximab, cyclophosphamide
Autoimmune autonomic neuropathy	Orthostatic hypotension, dry mouth, impaired pupillary responses, sexual dysfunction, urinary retention	Ganglionic AChR ($\alpha3\beta4$)	Autonomic testing	Pyridostigmine, symptomatic therapies, IVIG, plasmapheresis, steroids, immunosuppression
Paraneoplastic cerebellar degeneration (very rare)	Nystagmus, vertigo, dysarthria, ataxia	Hu, Yo, Tr (DNER), mGluR1	CSF analysis; brain MRI	Steroids, IVIG, rituximab, cyclophosphamide
Stiff Person syndrome and variants (*very rare)	Progressive muscle stiffness and spasms, exaggerated startle in some patients	GAD65, glycine receptor, amphiphysin	CSF analysis; brain MRI, spinal cord MRI	Benzodiazepines, baclofen, steroids, IVIG, rituximab

severity: symptomatic medication (ChE-Is, mostly pyridostigmine) can be sufficient for mildly affected patients, while those with disabling symptoms require steroids (prednisone or prednisolone) often in association with immunosuppressants, such as azathioprine, cyclosporine, or mycophenolate mofetil. Plasma-exchange and intravenous immunoglobulin (IVIG) are very effective in treating disease exacerbations.[8]

Thymoma-associated MG mainly occurs in subjects aged 40 to 60 years, with no gender prevalence; most patients show generalized weakness, often with a rapidly progressive course and early respiratory crises. In patients with thymoma, MG onset or deterioration can herald a tumor relapse.[9] As thymectomy can precipitate respiratory failure in severely affected patients, prompt and effective treatment is crucial in order to achieve stable control of MG symptoms before surgery.

Lambert Eaton myasthenic syndrome (LEMS) is a rare disorder of NMT characterized by muscle weakness and autonomic dysfunction. Clinical examination typically shows proximal muscle weakness, particularly of the legs, together with reduced or absent tendon reflexes; ocular and bulbar symptoms are less frequent than in MG; respiratory crises are uncommon.[10] Patients frequently complain of autonomic dysfunction as dry mouth, impotence, and constipation.

The pathophysiology of LEMS consists of a decreased quantal content, i.e., a reduced number of acetylcholine vesicles released by nerve depolarization, generally caused by Abs to the P/Q-type voltage-gated calcium channel (VGCC) on motor nerve membrane.[11] Such Abs are detected in approximately 85% of patients.[10] The autonomic symptoms may result from Ab-mediated inhibition of transmitter release from postganglionic parasympathetic and sympathetic neurons.[12] LEMS diagnosis is based on clinical features, serum VGCC-Ab detection, and electrodiagnostic studies showing a presynaptic NMT defect: a low-amplitude CMAP at rest, a decremental response on low-rate RNS, and a marked CMAP increment with high-frequency RNS or after exercise.[7] LEMS is paraneoplastic in 50% of patients, and is usually associated with small-cell lung carcinoma, while only a few cases with thymoma have been reported.[13] Symptomatic therapy with 3,4-diaminopyridine is the first option in these patients; immunosuppression along the same lines as in MG is indicated in cases with disabling symptoms; paraneoplastic LEMS typically improves with the treatment of the associated tumor.[8]