

# Paraneoplastic Syndromes Associated With Small Cell Lung Cancer

Leena Gandhi, MD, PhD, and Bruce E. Johnson, MD, Boston, Massachusetts

## Key Words

Paraneoplastic, ectopic, endocrine, neurologic syndrome, small cell lung cancer

## Abstract

Small cell lung cancer (SCLC) is the most frequent cancer histology associated with paraneoplastic syndromes. These syndromes are typically caused by ectopic hormone production or immune-mediated tissue destruction caused by neural antigen expression from cancer cells. This antigen expression induces the production of antibodies that cross-react with neural tissue. This article discusses the most common ectopic hormone and neurologic paraneoplastic syndromes and emphasizes the relationships among antigens, clinical syndromes, and outcomes. Although ectopic hormone production has been associated with extensive-stage disease and a poorer outcome, the antibody-mediated paraneoplastic syndromes are prognostic factors associated with more favorable outcomes. Both have the potential for improvement with cancer treatment. (*JNCCN* 2006;4:631–638)

Small cell lung cancer (SCLC) composes approximately 15% of lung cancers and is unique in both its aggressive behavior and its histologic features. SCLC is a rapidly growing cancer, and patients with extensive-stage SCLC treated with combination chemotherapy have an expected median survival of 9 to 11 months.<sup>1</sup>

The histologic characteristics of SCLC include features of aggressive growth, with a high mitotic rate, a high nuclear:cytoplasmic ratio, and high cellularity and necro-

sis.<sup>2</sup> Neuroendocrine morphology is common, with organoid, palisading, trabecular, or rosette-like growth patterns. Production of neuroendocrine markers can be detected using immunohistochemistry; neuroendocrine markers include chromogranin A, synaptophysin, CD56, and neuron-specific enolase. These neuroendocrine features are not unique to SCLC and can be seen in other pulmonary and extra-pulmonary tumors, probably as a result of the expression of proteins normally found in earlier, undifferentiated cells.<sup>3</sup>

In addition to these markers, which are not unique to SCLC, other factors may influence the actual production and secretion of endocrine peptides that cause paraneoplastic syndromes. For instance, the human achaete-scute homolog 1 (hASH1) is a neurogenic determinant expressed in fetal pulmonary neuroendocrine cells and in a subset of neuroendocrine tumors, including SCLC. The production of this transcription factor is associated with chromogranin A (protein making up granules associated with endocrine peptides), gastrin-releasing peptide, and calcitonin production in cancer cells.<sup>4</sup> Therefore, hASH1 may serve as one of the factors regulating expression and protein production of biologically active endocrine peptides. Another factor that may affect the incidence of immune-mediated neurologic paraneoplastic syndromes is the high rate of growth and subsequent apoptosis of SCLC tumor cells. This can lead to subsequent engulfment by antigen-presenting cells and an immune response that can predispose to immune-mediated paraneoplastic syndromes.<sup>5</sup> Alternatively, the neurologic differentiation of these tumor cells may result in expression of neural antigens in an abnormal context, which is then associated with generation of an immune response.

Paraneoplastic syndromes fall into 2 broad categories: those caused by ectopic production of biologically active peptides from the cancer cells themselves acting at distant sites, and those caused by antibody or cell-mediated immune responses generated against neural proteins expressed

From the Lowe Center for Thoracic Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, and Departments of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

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Correspondence: Bruce E. Johnson, MD, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Room D1234, 44 Binney Street, Boston, MA 02115. E-mail: bejohnson@partners.org

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by cancer cells. These immune responses can cross-react with normal neurons, causing tissue damage. These abnormal immune-mediated reactions can cause central or peripheral nervous system deficits that often arise before the cancer is diagnosed and can cause both morbidity and mortality apart from the cancer. This review

focuses only on the more common paraneoplastic syndromes of each type associated with SCLC and their relationship to SCLC therapy and outcome, with emphasis on new information generated within the past 5 years. Table 1 provides a more complete listing of known paraneoplastic syndromes in SCLC.

**Table 1. Paraneoplastic Syndromes Associated With Small Cell Lung Cancer**

ECTOPIC HORMONE –ASSOCIATED SYNDROMES			
<i>Clinical Syndrome</i>	<i>Incidence</i>	<i>SCLC-Produced Hormone</i>	
Ectopic Cushing syndrome	5%	ACTH	
Hyponatremia of malignancy	15%	CRH (rare)	
		AVP	
Hypertension	<1%	ANP	
Amenorrhea, galactorrhea	<1%	Renin	
Hyperamylasemia	<1%	prolactin, GH	
salivary amylase			
IMMUNE-MEDIATED NEUROLOGIC SYNDROMES			
<i>Clinical Syndrome</i>	<i>Incidence</i>	<i>Antibody</i>	<i>SCLC-Expressed Gene/Protein</i>
Lambert-Eaton myasthenic syndrome (LEMS)	1%	anti-VGCC	Synaptotagmin, MysB
Encephalomyelitis	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
Sensory neuropathy	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
Cerebellar degeneration	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
		anti-VJCC	Synaptotagmin, MysB
		anti-Ri	Nova-1
		anti-Yo	CDR-34
Retinopathy	<1%	anti-CAR	Recoverin
Stiff-person syndrome (encephalitis)	<1%	anti-amphiphysin	Amphiphysin
Opsoclonus, myoclonus	<1%	anti-Hu,	HuD, HuC, Hel-N1, N2
		anti-Ri	Nova-1

Abbreviations: ACTH, adrenocorticotropic hormone; ANP, atrial natriuretic peptides; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; GH, growth hormone; VGCC, voltage-gated calcium channel.

## Endocrine Paraneoplastic Syndromes

### Ectopic Cushing Syndrome

Abnormal hormone production in malignancy was first described in 1928 in a patient with symptoms and signs of hypercortisolism and a 1-cm oat-cell carcinoma.<sup>6</sup> These symptoms and signs included fatigue, moon facies, central obesity, and hirsutism—features that were previously reported as classic features of Cushing disease. However, when researchers analyzed patient data from 4 series and a literature review for specific clinical signs, they found that SCLC patients with ectopic Cushing syndrome more commonly presented with weight loss (83%), hypokalemia (87%), abnormal glucose tolerance (73%), and edema (58%) than with the more classic Cushingoid features of moon facies, central obesity, or hirsutism.<sup>7</sup> These symptoms and signs reflect rapid-onset hypercortisolism. SCLC patients with Cushing syndrome have plasma hydroxycorticosteroid (17-OHCS) and adrenocorticotropic hormone (ACTH) levels that are higher on average than those seen in the Cushing disease of pituitary origin.<sup>8</sup> This is different from patients with carcinoid tumor and ectopic Cushing syndrome, who present with more classic symptoms such as moon facies, abdominal striae, and hirsutism. The slower tumor growth in carcinoid tumors probably causes a more gradual increase in ACTH,<sup>9</sup> which may account for the differences in presentation. Notably, high circulating levels of glucocorticoids in patients with ectopic

Cushing syndromes of all types appear to predispose patients to developing severe, life-threatening infections that are often the cause of death in these patients.<sup>10,11</sup>

In addition to the higher levels of ACTH and 17-OHCS, patients with ectopic Cushing syndrome differ from patients with Cushing disease in the source of ACTH excess and associated feedback loops. Patients with ectopic Cushing syndrome usually do not show steroid output suppression with high-dose dexamethasone. This test and hormone level measurements are usually sufficient to diagnose the disorder, although sometimes petrosal sinus sampling after corticotropin-releasing hormone (CRH) stimulation is required to establish the source of ACTH (3:1 elevation of petrosal sinus: peripheral ACTH is typical in pituitary Cushing syndrome<sup>12</sup> as compared with 1:1 ratios seen in the ectopic Cushing syndrome).

Molecular studies of ACTH have shown that pro-opiomelanocortin (POMC) is a precursor to ACTH, synthesized in the pituitary and cleaved to form active ACTH. In many non-pituitary tissues, POMC transcripts made from alternate promoters are produced in small amounts.<sup>13</sup> However, high amounts of POMC transcripts of variable length have been seen in some neuroendocrine tumors. Presumably, local convertases can convert at least some of the protein produced from these altered transcripts into active ACTH.<sup>14</sup> Serum ACTH levels are elevated in up to 30% of SCLC patients,<sup>15</sup> but only 5% of these have evidence of Cushing syndrome.<sup>16-18</sup> This finding is consistent with the theory that at least some of the ACTH detected by radioimmunoassay is from altered transcripts or precursor proteins that do not produce active ACTH.

Several studies have shown that ectopic Cushing syndrome is more frequent in patients with extensive disease. These patients are less likely to show response to chemotherapy and more likely to experience premature death than patients without ectopic Cushing syndrome. A study of 90 patients with SCLC at M. D. Anderson Cancer Center who died within 90 days of the start of treatment included 11 patients with ectopic Cushing syndrome.<sup>10</sup> These patients had a shorter median survival (12 days) than patients with SCLC without ectopic Cushing syndrome (27 days). The cause of death in these 11 patients included infections or complications from infections rather than disease progression. Another single institution study<sup>18</sup> described 10 patients with SCLC and ectopic Cushing syndrome

with a median survival of 4 months (compared with a median survival time of 7–11 months among SCLC patients without ectopic Cushing syndrome).<sup>19</sup> Only 3 of the 10 patients with Cushing syndrome showed a partial or complete response to chemotherapy, and the clinical course was complicated by infection in 60%. However, survival was longer than 6 months in 3 patients whose hypercortisolism was controlled with either ketoconazole or bilateral adrenalectomy, and their clinical course paralleled that of their counterparts without Cushing syndrome.<sup>18</sup> This suggests that clinical control of hypercortisolism may ameliorate the adverse impact of Cushing syndrome on patient outcome.

Larger studies include a retrospective analysis of 545 patients with SCLC at Toronto General Hospital, which identified 23 patients with ectopic Cushing syndrome.<sup>16</sup> Of 6 patients treated with chemotherapy alone who showed tumor response, 4 also showed decreased ACTH levels. A second study at the same institution examined 15 consecutive patients treated with ketoconazole for ectopic Cushing syndrome, 9 of whom had SCLC. Six of these 9 patients treated concurrently with chemotherapy and ketoconazole showed decreases in ACTH, but only 1 of 6 patients evaluated for tumor response experienced a partial response; the others developed progressive disease. This study implies that improvement in hypercortisolism was primarily because of ketoconazole and that this improvement did not translate into improved chemotherapy response in these few patients.

Thus, tumor treatment alone can improve ectopic Cushing syndrome, but ketoconazole or other endocrine interventions such as metyrapone can be useful adjuncts to alleviating the metabolic and infectious complications of hypercortisolism before myelosuppressive therapy. Although infection control may improve initial survival, the association between ectopic Cushing syndrome and poor chemotherapy response persists despite treatment of hypercortisolism, a finding that requires further study.

### Hyponatremia of Malignancy

A more common paraneoplastic syndrome caused by ectopic hormone production is hyponatremia of malignancy, variably defined as serum sodium less than 130 to 135 mEq/L, which occurs in the setting of normal to increased urine osmolarity and dilute serum osmolarity. This occurs in 15% of SCLC patients, and these patients include more than 75% of those

diagnosed with this syndrome.<sup>20</sup> Although 82% of patients with hyponatremia present with low sodium at tumor diagnosis, few have clinical symptoms or signs caused by hyponatremia, including nausea, vomiting, lethargy, or seizures.<sup>21</sup>

Hyponatremia of malignancy has most commonly been associated with ectopic production of arginine vasopressin (AVP), otherwise known as antidiuretic hormone, from tumor cells. Several studies have compared levels of AVP from plasma or tumor cell lines, established from patients with SCLC and the degree of hyponatremia at presentation.<sup>21,22</sup> Not all patients with hyponatremia had inappropriately elevated plasma AVP or tumor-derived cell-line production of AVP.<sup>22</sup> In 1987, a patient without evidence of ectopic AVP production was found to have elevated plasma levels of atrial natriuretic peptide (ANP) detected by radioimmunoassay. The levels of ANP increased after water loading and hypertonic saline infusion. This result suggested that hypersecretion of ANP may have caused hyponatremia.<sup>23</sup> Several subsequent studies showed that tumor-derived cell lines expressed ANP mRNA, but again, no obvious relationship was seen between ANP production and hyponatremia in these patients.<sup>22,24,25</sup>

In 1997, Johnson et al.<sup>26</sup> reported a prospective study of patients with lung cancer to help define the relationship of AVP, ANP, and clinical manifestations of hyponatremia. Fifty patients with SCLC and non-small cell lung cancer (NSCLC) had plasma and urine electrolytes as well as plasma AVP, ANP, renin, angiotensin II, and aldosterone levels measured before and after a 500-mL saline infusion. All 11 patients who presented with hyponatremia had elevated plasma levels of AVP initially, and 3 also had elevated levels of ANP. Only AVP was highly associated with the presence of hyponatremia in this study. However, urinary sodium concentration increased during the saline infusion in proportion to the initial level of ANP, suggesting a role for ANP as well.

To define the role of these elevated peptides, a follow-up study was published in 2006.<sup>27</sup> In this study, 23 patients with lung cancer were prospectively studied over 4 days of fluid and sodium restriction. Seven of 9 patients with SCLC presented with a sodium level less than 135 mEq/L. Of these, 3 had elevated plasma levels of ANP and 2 had elevated plasma AVP. For the 2 patients with initially elevated plasma AVP levels, sodium values returned to normal over 4 days of

fluid and sodium restriction. The 3 patients with elevated ANP levels experienced reduced sodium over the same period, and persistent natriuresis was noted. Of the remaining 4 patients with no evidence of ectopic peptide production, no significant change in sodium level was observed over the 4-day study.

These study findings differ from those reported for a patient in 1987. This patient had elevated ANP with a sodium level that improved with fluid restriction (sodium restriction was not examined). The results suggest that hyponatremia is probably mediated by ectopic ANP production rather than AVP in a subpopulation of patients with SCLC and that fluid and salt restriction worsen hyponatremia in these patients.

Given the high prevalence of patients with SCLC and AVP-mediated hyponatremia, a general initial approach to treatment should still involve fluid restriction, with or without the addition of demeclocycline. Further studies are needed to assess the impact of giving salt and fluids to patients with hyponatremia caused by ectopic ANP production.

Regardless of the underlying cause of the hyponatremia, the most appropriate treatment is effective treatment of the cancer. Hyponatremia usually responds promptly to chemotherapy, and sodium is generally restored to near normal levels in 1 to 2 months. Patients frequently but not universally experience a decline in sodium at relapse, making declining sodium a tumor marker for cancer progression, although this has not been prospectively studied.

Hyponatremia itself is not a clear prognostic factor for patients with SCLC. Small studies have suggested that hyponatremia is associated with shortened survival in these patients.<sup>28,29</sup> However, other studies with larger numbers of patients with SCLC have found no effect of hyponatremia on outcome after chemotherapy or overall survival.<sup>21</sup>

## **Antibody-Mediated (Neurologic) Paraneoplastic Syndromes**

### **Lambert-Eaton Myasthenic Syndrome**

The most common neurologic paraneoplastic syndrome associated with SCLC is the Lambert-Eaton myasthenic syndrome (LEMS), which is present in approximately 1% to 3% of patients with SCLC at presentation. Patients with SCLC compose more than 40% of those with this syndrome,<sup>30</sup> but all present with slowly worsening proximal muscle weakness and

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fatigability with frequent autonomic dysfunction, including dry mouth and ptosis. This syndrome is characterized by a transient increase in strength with exercise, and EMG studies show decreased baseline muscle action potentiation that increases with repeated stimulations. This allows for clear-cut diagnosis. Autoantibodies directed against P/Q-type voltage-gated calcium channels (VGCC) on the surface of the tumor cells and at presynaptic nerve terminals have been identified as the causative agent of LEMS.<sup>31</sup> Antibody blockade of these channels at neuromuscular junctions causes a depletion of acetylcholinesterase, whose release is governed by these channels. This depletion results in the clinical symptoms described.

As with other neurologic paraneoplastic syndromes, the clinical symptoms of LEMS can predate the cancer diagnosis by months to years. This may be one reason why it is associated with limited-stage or localized SCLC. LEMS usually improves with effective chemotherapy but can also be effectively treated with plasmaphoresis, immunosuppression, intravenous immunoglobulin, and agents that stimulate transmitter release, such as 3, 4 diaminopyrimidine. LEMS has been shown to be a favorable prognostic factor in patients with SCLC and is associated with a longer median survival time of 24 months,<sup>32,33</sup> nearly twice that of patients without this syndrome.

This increased survival is presumed to be caused partly by the antecedent neurologic symptoms, which may lead to earlier diagnosis, and immune activity against the tumor itself. However, antibodies against VGCC are present in 2% to 7% of all patients with SCLC. A study involving 148 consecutive patients with SCLC showed no improved survival in patients with antibodies in the absence of clinical symptoms of LEMS.<sup>28</sup>

### Hu Antibody–Mediated Paraneoplastic Syndromes

Paraneoplastic neurologic syndromes characterized by inflammation and neuronal loss seen in patients with SCLC have been associated with the antibody HuAb (anti-HU). HuAb reacts against a family of RNA-binding proteins expressed in neurons and most cases of SCLC.<sup>34</sup> The 4 most common paraneoplastic neurologic syndromes are paraneoplastic cerebellar degeneration, limbic encephalitis, opsoclonus-myoclonus, and diffuse encephalitis with multifocal neurologic symptoms. Overall, more than 80% of patients with high-titer HuAb have SCLC.<sup>35</sup>

The factors that cause the clinical manifestation of one syndrome versus another are not clear, and not all cases of these defined syndromes are associated with the presence of detectable anti-Hu antibodies. This has led to the search for other potential neural antigens. For instance, a patient with subacute sensory neuropathy without HuAb was identified to have an autoantibody against Trk, a high-affinity nerve growth factor involved in neuronal survival and differentiation.<sup>36</sup>

The syndrome most commonly associated with HuAb is paraneoplastic encephalomyelitis and subacute sensory neuropathy syndrome. The name characterizes the multifocal nature of the disease, which can involve any part of the nervous system but most commonly presents with sensory and autonomic defects. The syndromes discussed in this section are subsets of this more generalized syndrome and are more variable in their association with detectable HuAb and SCLC.

Cerebellar degeneration usually presents with ataxia, nystagmus, dysarthria, and diplopia with or without more diffuse encephalitis. Progressive symptoms can cause a loss of the ability to ambulate within weeks to months. When present with associated HuAb in patients with SCLC, cerebellar degeneration is usually the cause of death.<sup>37</sup> The diagnosis is usually made clinically, but pathology often reveals inflammatory and lymphocytic infiltration and Purkinje cell loss.

Limbic encephalitis is less common. When it occurs, it is characterized primarily by mood and behavior changes with occasional seizures, and it progresses to dementia over weeks to months.<sup>38</sup> The diagnosis is made clinically, but EEG often shows generalized slowing and periodic epileptiform discharges. Pathology shows lymphocytic infiltrates and neuronal degeneration.

Opsoclonus-myoclonus is another rare neurologic syndrome. It presents with rapid conjugate eye movements, dysarthria, truncal ataxia, and myoclonus. Antibodies are not frequently identified. Pathology shows patchy lymphocytic infiltration throughout the cerebrum and cerebellum.

The pathologic findings in all of these syndromes suggest a cellular immune response against neuronal antigens. HuAb expression is associated with production of MHC class I antigens,<sup>34</sup> which may provide a cytotoxic T-cell response that is responsible for

the neuronal degeneration and demyelination in HuAb-associated syndromes. Expanded populations of tumor-specific cytotoxic T cells have been detected in patients with paraneoplastic cerebellar degeneration.<sup>39</sup>

Other neural antigens that have been identified in other paraneoplastic syndromes, such as recoverin in cancer-associated retinopathy, have also been seen to be immunopathogenic and cause an antibody-mediated cytotoxic response against neural targets.<sup>40</sup> This is different from LEMS, which results from steric antibody hindrance and not a direct cytotoxic effect.<sup>5</sup>

### Prognostic and Diagnostic Implications of Neurologic Syndromes for SCLC

The severity of these HuAb syndromes can vary among patients, but they rarely respond to any type of immunosuppression or plasmaphoresis. However, effective tumor treatment may stabilize or improve neurologic symptoms in patients with anti-Hu antibodies.<sup>41,42</sup> Rare cases of spontaneous regression of neurologic symptoms have been reported. Notably, in some of these cases, regression of the SCLC also occurred, supporting the idea that the paraneoplastic syndrome is linked to an immune response initially generated against the tumor.<sup>5,37,43</sup>

Furthermore, in a study of 196 patients without clinical evidence of any neurologic disease, the presence of HuAb in 27 patients was associated with more frequent complete response to therapy (55.6% vs. 19.6%) and longer survival (14.9 vs. 10.2 months).<sup>44</sup> Thus, unlike the anti-VGCC antibodies, a low titer of anti-Hu antibodies with no clinical neurologic symptoms was associated with an improved tumor outcome, which may be related to cytotoxic T cell-mediated immune response against the tumor.

The diagnosis of HuAb-mediated syndromes precedes the diagnosis of cancer by a mean of 4 to 7 months in most patients studied (200 in one series and 73 in another).<sup>41,42</sup> The frequent antecedent symptoms and the association of paraneoplastic neurologic syndromes with indolent and limited-stage tumors have led to investigations of the use of these syndromes in early detection and treatment of undiagnosed cancers and as markers for relapse. In a retrospective study of 24 patients with paraneoplastic encephalomyelitis and HuAb who already had an initial diagnosis of

tumor, paraneoplastic encephalomyelitis predicted progression or relapse in 21 (87%).<sup>41</sup>

Fluorodeoxyglucose positron-emission tomography (FDG-PET) scans have also been used to aid in early detection of cancer in patients who display signs of paraneoplastic neurologic syndromes. In a prospective study of 13 consecutive patients with anti-neuronal antibodies but no evidence of cancer, new tumor or tumor recurrence was diagnosed in 10 using FDG-PET with a 90% sensitivity, compared with a 30% sensitivity with concomitant CT.<sup>45</sup> In another prospective study involving 20 patients with paraneoplastic neurologic syndromes, FDG-PET detected tumor with an 83% sensitivity but only 25% specificity.<sup>46</sup> Nevertheless, both studies emphasize the idea that the presence of paraneoplastic neurologic syndromes provides a window of opportunity for early diagnosis that could make the difference in detecting limited versus extensive disease and thus afford an increased opportunity for curative treatment.

For both types of paraneoplastic syndromes, the presence of the autoantibody or ectopic hormone inconsistently correlates with the incidence of clinical manifestations. Thus, our understanding of these syndromes, although longstanding, is limited. Whether other unidentified tumor-specific factors or individual genome-specific factors are involved in determining when abnormal antibody or hormone production causes clinical symptoms, signs, and laboratory values remains to be determined. However, the presence of the syndrome or sometimes the presence of antibodies is useful in predicting response of the tumors to therapy, relapse, and survival. The correlation of paraneoplastic neurologic symptoms with improved tumor outcome indicates the potential usefulness of immune-mediated responses in tumor treatment itself, which should be further explored. Both types of syndromes have shown response to tumor treatment. Thus, as our tools for treating SCLC improve, so should outcomes of the associated paraneoplastic syndromes.

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