Paraneoplastic Syndromes Related to Lung Cancer

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Paraneoplastic syndromes (PNSs) are defined as signs or symptoms that occur as a result of organ or tissue damage at locations that are remote from the primary tumor site or metastases. Many cancers are associated with PNSs; however, small cell lung cancer (SCLC) is the most prevalent. In SCLC, the systems primarily affected by PNSs include the endocrine system, the neurologic system, and the integumental system. This article provides an overview of primary disorders and classical syndromes, as well as symptom management associated with each system. PNSs are rare, and the best approach is to treat the underlying tumor. Therefore, oncology nurses and other healthcare practitioners should be familiar with PNSs so that they can take prompt and proper courses of action, potentially leading to positive outcomes for patients.

Lung cancer is the leading cause of cancer-related deaths in the United States (Collins, Haines, Perkel, & Enck, 2007). Lung cancer is classified as either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) (Knop, 2005). SCLC, also known as oat cell lung cancer, is known to be a more aggressive lung cancer; it metastasizes rapidly to distant sites and is more often associated with paraneoplastic syndromes (PNSs) (Maghfoor & Perry, 2005).

Paraneoplastic Syndromes

PNSs are defined as signs or symptoms that occur as a result of organ or tissue damage at locations remote from the primary tumor site or metastases (Darnell & Posner, 2006). Although PNSs may be associated with many common malignancies, they are associated most commonly with lung cancer, specifically SCLC, although they also are seen in NSCLC (Rugo, 2007). Identified by categories rather than by specific systems, PNSs are classified as follows: nonspecific, rheumatologic, renal, gastrointestinal, hematologic, cutaneous, endocrine, or neurologic (Santacroce & Gagliardi, 2005). Thus, symptoms may occur based on the type of PNS that develops. Severity of symptoms is unrelated to the size of the primary tumor, and the symptoms often precede the diagnosis of lung cancer (Spiro, Gould, & Colice, 2007). The three PNS categories often associated with SCLC are endocrine, neurologic, and cutaneous (Rugo, 2007). Secrete a hormone or prohormone of a higher or lower molecular weight than hormones secreted by normal endocrine cells (Rugo, 2007). The most common endocrine disorders related to PNS are hypercalcemia, syndrome of inappropriate antidiuretic hormone (SIADH), and Cushing’s syndrome (Spiro et al., 2007) (see Table 1).

Endocrinologic Paraneoplastic Syndromes

Endocrinologic PNS results from an overproduction of specific hormones, which are strongly associated with specific types of tumors (Jameson & Johnson, 2008). Tumor cells may secrete a hormone or prohormone of a higher or lower molecular weight than hormones secreted by normal endocrine cells (Rugo, 2007). The most common endocrine disorders related to PNS are hypercalcemia, syndrome of inappropriate antidiuretic hormone (SIADH), and Cushing’s syndrome (Spiro et al., 2007) (see Table 1).

Hypercalcemia

Humoral hypercalcemia of malignancy most commonly is caused by overproduction of the parathyroid hormone–related protein (PTHrP) (Jameson & Johnson, 2008). PTHrP is structurally similar to the parathyroid hormone (PTH) and binds to PTH receptors (Jameson & Johnson, 2008). In addition, the PTHrP plays a role in skeletal development and also regulates cellular proliferation and differentiation in other tissues (Jameson & Johnson, 2008).
Nausea
TREATMENT
358
mg/dl should be added to the calcium level for an accurate
every decrease in albumin of 1 gm/dl below 4 gm/dl, then 0.8
plasma proteins (albumin) (Agraharkar, 2009). Therefore, for
interpreting calcium levels because calcium binds to 45% of
levels are greater than 14 mg/dl (Ruddy & Hochberg, 2008).
Symptoms typically occur when serum calcium
appear in a short period of time (McDonnell Keenan & Wick
ham, 2005). Symptoms of hypercalcemia may vary based on
serum calcium level and the rate at which serum calcium
resorption by acting on osteoblasts (Richerson, 2004).
Another substance that may play a role in hypercalcemia is
interleukin-1, which is an oestrocal-stimulating cytokine (Rich
son, 2004). Interleukin-1 is believed to stimulate the proliferation
of osteoblasts, which produces prostaglandin E, a potential mediator of bone resorption (Richerson, 2004). In addition, tumor necrosis factor, another cytokine, may increase osteoclastic resorption by acting on osteoblasts (Richerson, 2004).
The presenting symptoms of hypercalcemia may vary based on serum calcium level and the rate at which serum calcium levels become elevated (Body, 2004; Stewart, 2005). Hypercalcemia of malignancy develops rapidly, so symptoms may appear in a short period of time (McDonnell Keenan & Wickham, 2005). Symptoms typically occur when serum calcium levels are greater than 14 mg/dl (Ruddy & Hochberg, 2008). Nurses should take into account serum albumin levels when interpreting calcium levels because calcium binds to 45% of plasma proteins (albumin) (Agraharkar, 2009). Therefore, for every decrease in albumin of 1 gm/dl below 4 gm/dl, then 0.8 mg/dl should be added to the calcium level for an accurate value (Agraharkar, 2009). General symptoms of hypercalcemia include nausea, vomiting, dehydration, abdominal pain, constipation, polyuria, polydipsia, confusion, weakness, lethargy, and irritability (Spiro et al., 2007). In addition, cardiac arrhythmias may occur as excess calcium affects cardiac muscle contractility, cell membrane permeability, and conduction of electrical impulses through the heart (Armstrong, 2005).

If a patient presents with hypercalcemia, whether mild or severe, the primary goal is to restore fluid and electrolyte balance (McDonnell Keenan & Wickham, 2005). This is done through rehydration with IV 0.9% normal saline (Richerson, 2004). The rate of fluid administration is based on the severity of hypercalcemia, dehydration, and the patient’s cardiovascular tolerance for volume expansion (McDonnell Keenan & Wickham, 2005). If fluid overload is a major concern, a loop diuretic, most commonly furosemide, may be added to enhance the renal excretion of calcium (McDonnell Keenan & Wickham, 2005; Richerson, 2004).
Bisphosphonates are agents that inhibit osteoclast activity, which, in turn, decreases serum calcium levels (Hempill, 2007). According to Stewart (2005), IV bisphosphonates have been shown to be the safest and most effective agents used to treat hypercalcemia associated with malignancies. Response to bisphosphonate therapy takes approximately two to four days; therefore, therapy should be initiated as soon as hypercalcemia is discovered (Stewart, 2005).
For management of mild hypercalcemia, administration of a regularly scheduled phosphate is the preferred form of anti-hypercalcemic therapy (Richerson, 2004). Most authors have defined mild hypercalcemia as a calcium level less than 12 mg/dl (McDonnell Keenan & Wickham, 2005; Stewart, 2005). An inverse relationship exists between phosphorus and calcium levels and is regulated by the PTH (Kaplan, 2006). Therefore, when hypophosphatemia is corrected, so is hypercalcemia.
Calcitonin is a naturally occurring hormone in the body that inhibits bone resorption and increases excretion of calcium from the system (Hempill, 2007). Calcitonin treatments may be used when needed for rapid correction of severe hypercalcemia and may be given in combination with rehydration and diuresis (Potts, 2005). Calcitonin is a subcutaneous or intramuscular injection that is given in doses of 4–8 IU/kg, every 6–12 hours for two days, and it typically is given with bisphosphonates (Richerson, 2004).
Hemodialysis, although used rarely, may be considered the treatment of choice in severe hypercalcemic states, when hydration and bisphosphonate treatments do not incur a rapid response or are not available (Jameson & Johnson, 2008). Hypercalcemia is considered severe when calcium levels range from 14–16 mg/dl (McDonnell Keenan & Wickham, 2005; Stewart, 2005). Large amounts of phosphate may be lost during hemodialysis; therefore, phosphate concentrations should be measured after every dialysis treatment, and supplements should be added to the patient’s diet or to the dialysis fluid when indicated (Potts, 2005).

Oncology nurses, patients, and family members must be able to recognize and adequately manage hypercalcemia when signs and symptoms appear. Although PNSs are rare, the best treatment is to identify and treat the underlying tumor (Thomas, Kwok, & Edelman, 2004). Therefore, clinicians must know when

### Table 1. Common Endocrine Disorders Related to Paraneoplastic Syndromes in Lung Cancer

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>SYMPTOMS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia</td>
<td>Nausea</td>
<td>Rehydrate with 0.9% normal saline with or without loop diuretic therapy</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
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<tr>
<td></td>
<td>Dehydration</td>
<td></td>
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<tr>
<td></td>
<td>Abdominal pain</td>
<td>IV bisphosphonates</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>Phosphate therapy for mild hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Polyuria</td>
<td>Hemodialysis for severe hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Polydipsia</td>
<td>Calcitonin injections</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
<td></td>
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<tr>
<td></td>
<td>Lethargy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Syndrome of inappropriate antidiuretic hormone</td>
<td>Weakness</td>
<td>Administration of demeclocycline or conivaptan</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>Strict monitoring of input and output</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Infusion of 3% hypertonic saline solution or normal saline with furosemide (for severe hyponatremia)</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased level of consciousness</td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Proximal myopathy</td>
<td>Resection of the primary tumor</td>
</tr>
<tr>
<td></td>
<td>Moon facies</td>
<td>Treatment for the underlying malignancy</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>Use of metyrapone, ketoconazole, or octreotide</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from Armstrong, 2005; Jameson & Johnson, 2008; McDonnell Keenan & Wickham, 2005; Potts, 2005; Richerson, 2004; Spiro et al., 2007; Stewart, 2005.
and which diagnostic tests to order based on a patient’s history and symptoms. Typically, serum calcium levels confirm a diagnosis of hypercalcemia (McDonnell Keenan & Wickham, 2005). However, a complete metabolic panel, phosphorus, magnesium, blood urea nitrogen, creatinine levels, and urine calcium levels are among the other laboratory tests on which healthcare providers should focus. In addition, testing albumin levels should be considered. Results from all of the diagnostic tests may help oncology nurses and other clinicians to rule out other potential causes of hypercalcemia, such as hyperparathyroidism or acute renal failure. Once PNS is considered to be part of the differential diagnosis, prompt and proper courses of action should be taken, which may result in more positive outcomes for patients.

**Syndrome of Inappropriate Antidiuretic Hormone**

SIADH is an electrolyte disorder that is associated with neurolgic complications; another name for the condition is water intoxication. It is commonly associated with lung cancer as well as other tumor-related conditions, such as tumors of the head, neck, and breast (Onitilo, Kio, & Doi, 2007). Armstrong (2005) defined SIADH as the presence of hyponatremia with plasma hypo-osmolality and concentrated urine greater than 20mEq/L. SIADH may cause hyponatremia; mild hyponatremia is defined as a serum sodium level less than 135 mEq/L; moderate hyponatremia, less than 125 mEq/L; and severe hyponatremia, less than 125 mEq/L (Onitilo et al., 2007).

A variety of theories exist regarding the mechanisms that cause SIADH. Several hormones, including atrial natriuretic peptide hormone, have been suggested as contributing to SIADH (Spiro et al., 2007). Antidiuretic hormones (ADHs) are elevated because of the abnormal production of ADH or ADH-like substances by cancer cells (Thomas et al., 2004). However, the production of vasopressin hormone from an atypical source may be another cause (Onitilo et al., 2007).

Hyponatremia may take weeks or months to develop, and most patients with this ectopic vasopressin secretion are asymptomatic (Jameson & Johnson, 2008). Smoking, nicotine, stress, pain, nausea, and morphine, which can increase vasopressin production, also may contribute to SIADH (Armstrong, 2005).

The symptoms of SIADH rarely are present if plasma sodium levels are greater than 125 mEq/L (Onitilo et al., 2007). The symptoms include weakness, lethargy, nausea, confusion, and an unexplained decreased level of consciousness (Spiro et al., 2007). Nausea and malaise may be the earliest signs of SIADH, when plasma sodium levels fall to 125–130 mEq/L; seizures and coma may occur in extremely severe hyponatremic states when levels are below 120mEq/L (Onitilo et al., 2007).

The rapid correction of hyponatremia may lead to the development of osmotic demyelination syndrome, which may cause acute paralysis, blindness, and other neurologic symptoms; therefore, SIADH should be corrected at a gradual rate (Onitilo et al., 2007). The strict monitoring of liquids, both IV and oral, as well as medications such as demeclocycline or conivaptan, may correct hyponatremia (Jameson & Johnson, 2008). Demeclocycline corrects hyponatremia by inhibiting vasopressin (an ADH) action on renal distal tubules (Jameson & Johnson, 2008). Conivaptan is a nonpeptide V2-receptor agonist, which causes an antinatriuretic effect (Jameson & Johnson, 2008), that is, it enhances free water excretion without increasing renal excretion of sodium or potassium (Li-Ng & Verbalis, 2009). In severe hyponatremic states, hypertonic (3%) or normal saline with furosemide may be infused to relieve water retention (Jameson & Johnson, 2008). According to Richerson (2004), the rate of serum sodium elevation should be corrected at 0.5–1 mEq/L per hour. However, cause, duration, symptoms, renal function, and potassium levels are factors to be considered and will contribute to the rate of correction (Onitilo et al., 2007).

If conditions that mimic SIADH (such as cardiac, renal, adrenal, or thyroid disorders) can be ruled out, then SIADH is the most likely cause of the symptoms (Mazzone & Arroliga, 2005). Therefore, clinicians must act promptly, ordering the correct tests (i.e., serum sodium level, serum osmolality, urine osmolality, and urinary sodium concentration). Based on any abnormal test results, oncology nurses may work on correcting electrolyte imbalances. Knowledge of PNSs will help to prevent misdiagnosis of the problem, as clinicians will be looking for the underlying causes of SIADH.

**Cushing’s Syndrome**

In patients with lung cancer, the ectopic production of adrenocorticotropic hormone (ACTH) is the most common cause of Cushing’s syndrome (Spiro et al., 2007). ACTH stimulates the adrenal cortex to produce excessive amounts of glucocorticoids, which leads to the development of Cushing’s syndrome (Armstrong, 2005). Ectopic ACTH production is caused by the increased expression of the pro-opiomelanocortin gene, which along with other peptides and hormones, encodes ACTH (Jameson & Johnson, 2008). However, endogenous secretion of corticotropin is more common than ectopic secretion (Newell-Price, Bertagna, Grossman, & Nieman, 2006).

The symptoms of Cushing’s syndrome are weakness, muscle wasting, drowsiness, confusion, dependent edema, moon facies, hypokalemic alkalosis, hyperglycemia, and possible psychosis, although patients with SCLC rarely have all of the classic signs (Armstrong, 2005; Spiro et al., 2007). The most common symptoms are proximal myopathy, moon facies, hypokalemia, and hyperglycemia (Armstrong, 2005). In addition, patients may experience personality changes such as depression or emotional lability because of excess cortisol (Jameson & Johnson, 2008).

To confirm a diagnosis of Cushing’s syndrome, a plasma cortisol level and a 24-hour urinary-free cortisol level are measured (Armstrong, 2005). The 24-hour urinary-free cortisol level measures the level of circulating free cortisol (Newell-Price et al., 2006). If the 24-hour urinary-free cortisol level is elevated with a high serum ACTH level, PNS is confirmed (Jameson & Johnson, 2008).

Effective treatment of Cushing’s syndrome is the resection of the primary tumor or other treatment of the underlying malignancy (Jameson & Johnson, 2008). Though this may reduce ACTH levels, rarely do levels return to normal (Jameson & Johnson, 2008). Most patients with SCLC with Cushing’s syndrome respond poorly to chemotherapy because of the extent of lung cancer (Spiro et al., 2007). Other treatment options may include medications such as metyrapone, ketoconazole, or octreotide (Armstrong, 2005).
PNSSs are rare, so the importance of clinicians' awareness of the syndromes in lung cancer cannot be minimized, because the best course of action includes treatment of the underlying tumor (Spiro et al., 2007). Proper knowledge of Cushing’s syndrome is important to expediently diagnose and treat the condition and allow proper management of the disease.

Paraneoplastic Neurologic Disorders

According to Darnell and Posner (2006), paraneoplastic neurologic disorders (PNDs) are acute or subacute, progress over weeks to months, and often occur in those who are not known to have cancer or in whom cancer may not yet be detected. PNDs are almost always associated with SCLC (Spiro et al., 2007).

Most PNDs are thought to be immune mediated (Armstrong, 2005). They are associated with antibodies directed against antigens expressed by the tumor and the nervous system (Honnorat & Antoine, 2007). The presence or absence of the paraneoplastic antibodies, as well as their type, helps to define the different subtypes of PND (Honnorat & Antoine, 2007). Positive tests for any of the antibodies strongly indicates the presence of a PND (Darnell & Posner, 2006). Many different antibodies are specific for each type of PND, and although patients have been found to have more than one antibody present, one antibody usually predominates (Darnell & Posner, 2006).

PNDs are classified into classical or nonclassical syndromes (Dalmau, 2007). Classical PND syndromes are those that are more frequently associated with cancer or have characteristics that suggest a paraneoplastic etiology, such as the presence of antibodies (Dalmau, 2007). Nonclassical PND syndromes are those that result from paraneoplastic mechanisms but occur more frequently in the absence of cancer (Dalmau, 2007). PNDs may affect many different areas, including the central nervous system, the peripheral nervous system, the neuromuscular junction, or the muscle (Honnorat & Antoine, 2007). Lambert-Eaton myasthenic syndrome (LEMS), subacute cerebellar degeneration (SCD), and sensory peripheral neuropathy (SPN) are three neuromuscular PNSs that are strongly associated with SCLC (Rugo, 2007) (see Table 2).

Lambert-Eaton Myasthenic Syndrome

LEMS is known as a paraneoplastic antibody–mediated autoimmune disorder (Armstrong, 2005) and is the most common of the classical PNSs (Darnell & Posner, 2006). SCLC is the cancer most associated with LEMS, and LEMS is strongly associated with those who have a history of smoking and who have the absence of the human leukocyte antigen-B genotype (de Beukelaar & Sillevis Smitt, 2006).

The symptoms of LEMS include weakness in the lower extremities, fatigue, diminished or absent deep tendon reflexes, and respiratory weakness and usually precede the diagnosis of cancer (Darnell & Posner, 2006; de Beukelaar & Sillevis Smitt, 2006). Additional symptoms that affect cranial nerve function include blurred vision, diplopia, or ptosis; symptoms affecting the autonomic nervous system include dry mouth and constipation (Darnell & Posner, 2006).

The diagnostic test used to determine whether a patient has LEMS is electromyography, which measures the action potential of the muscles (Armstrong, 2005). In addition, those with paraneoplastic LEMS always harbor P/Q type voltage-gated calcium channel (VGCC) antibodies in the serum (Darnell & Posner, 2006). Antibodies against P/Q VGCC impair conduction at the presynaptic level of the neuromuscular junction, thus causing weakness, fatigue, and other related symptoms (Ruddy & Hochberg, 2008).

The common approach for LEMS related to SCLC is treatment of the tumor, which may improve neurologic symptoms (Darnell & Posner, 2006). In addition, medications such as 3, 4-diamino-

| Table 2: Common Neurologic Disorders Related to Paraneoplastic Syndromes in Lung Cancer |

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>SYMPTOMS</th>
<th>ASSOCIATED ANTIBODIES</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>Weakness to lower extremities</td>
<td>P/Q type voltage-gated calcium channel (P/Q VGCC)</td>
<td>Treatment of the tumor 3,4-diaminopyridine</td>
</tr>
<tr>
<td>Sensory peripheral neuropathy</td>
<td>Pain</td>
<td>Anti-Hu (ANNA-1) Anti-myelin-associated glycoprotein (MAG) Anti-CV2 (CRMP-5)</td>
<td>Early detection Treatment of the underlying neoplasm</td>
</tr>
<tr>
<td>Subacute cerebellar degeneration</td>
<td>Nausea Vomiting Dizziness Lack of coordination when walking Ataxia of gait, limbs, and trunk Dysarthrias Nystagmus Hearing loss Dysphagia Mental status changes</td>
<td>Anti-Hu (ANNA-1) Anti-Yo (PCA-1) Anti-CV2 (CRMP5)</td>
<td>Difficult to treat Improvements seen with • Plasma exchange • Steroids • Immunoglobulins • Rituximab</td>
</tr>
</tbody>
</table>

Note: Based on information from Darnell & Posner, 2006; de Beukelaar & Sillevis Smitt, 2006; Honnorat & Antoine, 2007; Ruddy & Hochberg, 2008.
OP: DAP have been used for symptomatic treatment because DAP facilitates presynaptic acetylcholine release, thus improving symptoms (Darnell & Posner, 2006; de Beukelaar & Sillevis Smitt, 2006). However, if the treatment is unsuccessful in managing symptoms, plasma exchange or immunosuppressive therapy may be used (Darnell & Posner, 2006; de Beukelaar & Sillevis Smitt, 2006). Ultimately, treatment of LEMS must be tailored to the individual based on the severity of symptoms, underlying disease, and previous response to treatment (de Beukelaar & Sillevis Smitt, 2006). For those with LEMS related to PNS, treatment of the primary tumor leads to neurologic improvement (de Beukelaar & Sillevis Smitt, 2006). Clinicians who are aware of the signs and symptoms of LEMS may diagnose and properly treat both LEMS and the cancer, resulting in optimal outcomes for patients.

Subacute Cerebellar Degeneration

SCD is the most frequently seen PNS affecting the brain (Turker, Unsal, & Onar, 2007). It is defined by the rapid development of severe pan-cerebellar dysfunction from an extensive loss of Purkinje neurons in areas where other cerebellar neurons are preserved (Honnorat & Antoine, 2007). The anti-Yo antibody specifically damages the Purkinje cells of the cerebellum and often is found in the serum and cerebral spinal fluid of patients with SCD (Turker et al., 2007).

SCD may be associated with many types of carcinomas but, as with other PNSs, often is associated with SCLC (Darnell & Posner, 2006). As with LEMS, symptoms of SCD often occur prior to the diagnosis of cancer, and the cancer usually is discovered within one year of onset of SCD symptoms (Darnell & Posner, 2006).

Symptoms of SCD are acute and include nausea, vomiting, dizziness, and lack of coordination when walking (de Beukelaar & Sillevis Smitt, 2006). This lack of coordination progresses to ataxia of gait, limbs, and trunk, with dysarthrias and nystagmus. According to de Beukelaar and Sillevis Smitt (2006), signs and symptoms typically are limited to the cerebellum and cerebellar pathways. However, more widespread symptoms such as hearing loss, dysphagia, and mental status changes often occur in those diagnosed with SCLC (Darnell & Posner, 2006; de Beukelaar & Sillevis Smitt, 2006). Once SCD is stabilized, most patients cannot walk without support, nor can they sit unsupported (Darnell & Posner, 2006). In addition, writing is impossible, and independent eating is difficult (Darnell & Posner, 2006).

The diagnosis of paraneoplastic SCD is confirmed through positive testing of specific antineuronal antibodies; the three most common antibodies associated with SCD are anti-Hu (ANNA-1), anti-Yo (PCA-1), and anti-CV2 (CRMP5) (de Beukelaar & Sillevis Smitt, 2006; Honnorat & Antoine, 2007). The type of antibody assists in detecting the underlying neoplasm (de Beukelaar & Sillevis Smitt, 2006). However, 30%–40% of patients with paraneoplastic cerebellar degeneration do not harbor any antineuronal antibodies (Dalmau, 2007).

The other tests that should be conducted when neurologic symptoms occur include magnetic resonance imaging (MRI) of the brain with gadolinium, computed tomography (CT) of the brain with and without contrast, and a lumbar puncture to test cerebral spinal fluid (Armstrong, 2005). Initially, MRI and CT scans are normal, but as SCD progresses, scans later reveal cerebellar atrophy, as well as a dilated fourth ventricle (Armstrong, 2005; de Beukelaar & Sillevis Smitt, 2006). Because the cerebellum is a common target for most paraneoplastic immune responses, testing of the cerebrospinal fluid often shows abnormalities commonly found in neurologic PNS (Dalmau, 2007). The results of cerebrospinal fluid tests often show mild lymphocytic pleocytosis, with elevated protein levels and immunoglobulin G antibody levels within the first weeks to months of SCD (Armstrong, 2005; de Beukelaar & Sillevis Smitt, 2006). In addition, an increase in oligoclonal bands, which are specific gamma globulin proteins, may be present (de Beukelaar & Sillevis Smitt, 2006). As SCD progresses, the cerebrospinal fluid may become acellular (Darnell & Posner, 2006).

Paraneoplastic SCD is one of the most difficult syndromes to treat, and the outcome is generally poor (Dalmau, 2007; de Beukelaar & Sillevis Smitt, 2006). This is primarily because once Purkinje cells are destroyed, treatment will have little effect (Darnell & Posner, 2006). The prompt diagnosis and treatment of SCD can stabilize the disorder, which can prevent further involvement of the nervous system (Dalmau, 2007). Improvements have been made with the use of plasma exchange, steroids, immunoglobulins, and rituximab (de Beukelaar & Sillevis Smitt, 2006). However, whether improvements were spontaneous or in association with treatment is unclear (de Beukelaar & Sillevis Smitt, 2006).

Oncology nurses and other clinicians who know that SCD is associated most commonly with lung cancers understand that early detection and treatment of the underlying neoplasm offer the best chance of stabilizing the neurologic symptoms (de Beukelaar & Sillevis Smitt, 2006). Early detection may help patients achieve better quality of life.

Sensory Peripheral Neuropathy

SPN is caused by primary damage from inflammation to the sensory nerve cell body of the dorsal root ganglia (Dalmau, 2007). A wide range of sensory neuropathies can result from antibodies binding to sensory fibers, which then induce inflammation, leading to demyelination (Ruddy & Hochberg, 2008). The anti-Hu antibody is the most frequent antibody associated with paraneoplastic SPN (de Beukelaar & Sillevis Smitt, 2006). The anti-myelin-associated glycoprotein and anti-CV2/CRMP5 antibodies have been linked with SPN as well (Ruddy & Hochberg, 2008).

The symptoms of SPN begin with pain and paresthesia, followed by clumsiness and an unsteady gait (de Beukelaar & Sillevis Smitt, 2006). The pain eventually turns into numbness, limb ataxia, and pseudoathetotic movements, or abnormal writhing of the hands (Honnorat & Antoine, 2007). Symptoms tend to be progressive, are asymmetric in distribution, and usually involve the arms, the trunk, and sometimes the face (Dalmau, 2007).

Electrophysiology studies show that patients with SPN have small-amplitude or absent sensory nerve action potentials (Dalmau, 2007; Honnorat & Antoine, 2007). Typically, motor conduction is preserved (Dalmau, 2007). However, in some
cases, motor conduction velocities may be mildly decreased (de Beukelaar & Sillevis Smitt, 2006; Vedeler et al., 2006). In addition, nerve biopsies may be conducted to differentiate SPN from vasculitic neuropathies; however, this rarely needs to be done (de Beukelaar & Sillevis Smitt, 2006; Vedeler et al., 2006).

In most cases, immunotherapy for treatment of SPN has been found to be ineffective (de Beukelaar & Sillevis Smitt, 2006). Early detection and treatment of the underlying neoplasm best stabilize the symptoms (de Beukelaar & Sillevis Smitt, 2006). Those with a low titre of anti-Hu antibodies tend to have early-stage tumors and good responses to chemotherapy, which leads to improved outcomes (Turker et al., 2007). In addition, chemotherapy treatment may be recommended in patients who have not yet had a definitive diagnosis of cancer, test positive for the anti-Hu antibody, are older than 50 years, and have a history of smoking (de Beukelaar & Sillevis Smitt, 2006). This is because SPN, like other PNSs, begins to show clinical symptoms prior to the finding of a malignant tumor (Turker et al., 2007). On average, a tumor is discovered three to eight months after symptoms appear (de Beukelaar & Sillevis Smitt, 2006; Rudnicki & Dalmau, 2005).

Clinicians who are aware of paraneoplastic SPN may make a significant difference in a patient’s prognosis. As with other PNSs, symptoms occur prior to tumor diagnosis. Clinicians who can quickly rule out the many different diagnoses of neuropathy, such as autoimmune disorders and vasculitis, may achieve more positive outcomes for patients, because early diagnosis may lead to a more optimal treatment response.

**Cutaneous Paraneoplastic Syndromes**

Dermatomyositis is an inflammatory muscle disease associated with specific characteristic skin eruptions (Ghfir & Rais, 2007) (see Table 3). Affecting both the neuromuscular system and the skin, dermatomyositis is classified as a neuromuscular PNS as well as an integumentary PNS (Rugo, 2007). The cutaneous characteristics of dermatomyositis include a heliotrope rash to the periorbital skin, erythematous scaly plaques on the dorsal side of the hands, periungual telangiectasia, and photosensitive poikilodermatous eruptions (Honnorat & Antoine, 2007). In addition, weakness to the proximal muscles (thighs and shoulders) may be accompanied by cutaneous symptoms (Ghfir & Rais, 2007). The myopathy tends to be symmetrical and slowly progresses over a period of weeks to months (Honnorat & Antoine, 2007). Initial complaints may include myalgia, weakness, and fatigue, as evidenced by an inability to climb stairs or to rise from a sitting to standing position, as well as an inability to raise the arms to groom hair or to shave (Callen & Wortmann, 2006). In most cases, the heliotrope rash (a purplish discoloration of the eyelids) precedes the appearance of proximal muscle weakness (de Beukelaar & Sillevis Smitt, 2006). Dermatomyositis affects adults aged 40–60 years and is more frequent in men (Ghfir & Rais, 2007).

A diagnosis of dermatomyositis precedes a malignant diagnosis approximately 70% of the time (Ghfir & Rais, 2007). Many autoantibodies and myositis-associated antibodies have been recognized with dermatomyositis, but none has been linked to tumors (Honnorat & Antoine, 2007). According to de Beukelaar and Sillevis Smitt (2006), antineuronal antibodies to the Mi-2 protein complex are found in 35% of cases. Patients with dermatomyositis are found to have elevated serum creatinine kinase levels and electromyographic evidence of myopathy (de Beukelaar & Sillevis Smitt, 2006). In addition, a skin or muscle biopsy may assist in a definitive diagnosis of dermatomyositis, and a CT scan or MRI may be helpful in confirming and determining the type of inflammatory myopathy that may be occurring (de Beukelaar & Sillevis Smitt, 2006).

The primary approach to paraneoplastic dermatomyositis is treatment of the underlying tumor (Honnorat & Antoine, 2007). Therapy for the myopathy includes corticosteroids and azathioprine (de Beukelaar & Sillevis Smitt, 2006). To treat cutaneous symptoms, patients should avoid sun exposure and use sunscreens; in addition, topical corticosteroids, antimalarial agents, methotrexate, mycophenolate mofetil, and immunoglobulins may be used (Ghfir & Rais, 2007).

For optimal results, oncology nurses and other healthcare providers must be well informed about the signs and symptoms of neurologic PNSs so that they can promptly diagnose and treat the symptoms. According to Darnell and Posner (2006), if a patient has developed an acute or subacute neurologic disability that is not explained through physical examination or laboratory tests, PND should be suspected. Clinicians must conduct a thorough neurologic examination with proper diagnostic tests, both of which are essential for identifying the lung cancer related to the neurologic disorders (Turker et al., 2007). Because of the diagnostic challenges that occur with neu-

| Table 3. Common Cutaneous Disorders Related to Paraneoplastic Syndromes in Lung Cancer |
|---------------------------------|---------------------------|---------------------|
| **DERMATOMYOSITIS**             | **CHARACTERISTICS**       | **TREATMENT**       |
| Cutaneous                       | Heliotrope rash to periorbital skin | Treatment of underlying tumor |
|                                 | Erythematous scaly plaques to dorsal side of hands | Avoidance of sun exposure |
|                                 | Periungual telangiectasia | Sunscreen use |
|                                 | Photosensitive poikilodermatous eruptions | Topical corticosteroids |
|                                 |                           | Antimalarial agents |
|                                 |                           | Methotrexate |
|                                 |                           | Mycophenolate mofetil |
|                                 |                           | Immunoglobulin therapy |
| Myopathic                       | Myalgia                   | Treatment of the underlying tumor |
|                                 | Weakness                  | Corticosteroids |
|                                 | Fatigue                   | Azathioprine |
|                                 | Decrease in activities of daily living | |

*Note. Based on information from Callen & Wortmann, 2006; de Beukelaar & Sillevis Smitt, 2006; Ghfir & Rais, 2007; Honnorat & Antoine, 2007.*
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Implications for Nursing

For oncology nurses and other healthcare providers, taking a thorough history is essential, not only to identify abnormal findings but also to establish a positive rapport with patients. PNSs are rare, diagnosis is difficult, and patients often are misdiagnosed (Honnorat, 2006). Healthcare providers must be educated about PNSs because early detection and treatment of the underlying tumor are the best therapies to halt or reverse the syndrome (Raza & Tandar, 2003). Therefore, oncology nurses should be astutely aware of what PNSs are and the symptoms that may manifest. When symptoms do present, knowledge of a patient’s past tobacco use and environmental factors, such as family members who may have smoked or past employment where smoking was permitted, may assist clinicians in considering PNS in the differential diagnosis. In addition, if symptoms develop, knowledge of past malignancies may assist in accurate assessment of and testing for recurrence.

When patients present with PNSs, oncology nurses must have an understanding of the proper interventions and treatments for optimal outcomes. In addition, medication assessments can avoid any interactions or substances that may contribute to PNS. For example, thiazides or lithium may potentiate hypercalcemia (Kaplan, 2006), and side effects of chemotherapy may cause vomiting, which may alter electrolyte levels and cause lethargy. Educating patients and families about PNSs, which side effects to be aware of, and other potential symptoms that may present with further progression of disease is important as well.

Patient safety is a major concern, especially when patients present with bilateral lower-extremity weakness, fatigue, or confusion. Referral to physical therapy may be required when assistive devices (e.g., cane, walker, wheelchair) are needed. Nurses must educate patients and their caretakers to avoid sedating medications if possible because they may further alter the cognitive level. Therefore, when patients present with complaints of pain, insomnia, or anxiety, clinicians must carefully evaluate all treatment options, as many medications may contribute to cognitive changes and falls.

Oncology nurses also may be confronted with end-of-life considerations when treatments for either the malignancy or the PNS are no longer effective. In such cases, detailed discussions explaining why therapies are no longer effective must be addressed. In addition, nurses and other healthcare providers must provide options to patients and their families and may refer them to a social worker or psychiatric nurse practitioner, or discuss options of hospice with patients. In so doing, nurses may assist in improving the quality of life for patients who are in the end stages of their disease.

Conclusion

Because PNSs are rare, education and research in this field must be ongoing. As more oncology nurses and other healthcare providers are educated about PNSs and additional research is conducted, patients may be diagnosed earlier in the course of their disease. The long-term goals are early detection, proper management, and more positive outcomes for patients.

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Honnorat, J. (2006). Onconeural antibodies are essential to diagnose and discuss options of hospice with patients. In so doing, nurses refer them to a social worker or psychiatric nurse practitioner, must provide options to patients and their families and may discuss syndromes mentioned in this article, then PNS is suggestive, and tumor recurrence should be explored (Rudnicki & Dalmau, 2005).


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