Paraneoplastic syndromes in lung cancer

Review Article

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Key words: Anemia, antidiuretic hormone, autoantibody, cachexia, cancer, chemotherapy, clubbing, Cushing, dermatomyositis, hypertrophic pulmonary osteoarthropathy, hypercalcaemia, Lambert-Eaton, lung, neurologic, paraneoplastic, syndrome

Abbreviations: Adrenocorticotrophic hormone, (ACTH); antidiuretic hormone, (ADH); atrial natriuretic peptide, (ANP); cancer procoagulant, (CP); ciliary neutropic factor, (CNTF); cyclic adenosine monophosphate, (cAMP); granulocyte colony stimulating factor, (G-CSF); Granulocyte macrophage- colony stimulating factor, (GM-CSF); hypertrophic pulmonary osteoarthropathy, (HPO); hypothalamic-pituitary-adrenal ‘HPA); interferon, (IFN); interleukin, (IL); Lambert-Eaton myasthenic syndrome ‘LEMS); lipid mobilizing factor, (LMF); low molecular weight heparin, (LMWH); non-small-cell lung cancer, (NSCLC); Palmo-plantar hyperkeratosis, (PPH); parathyroid hormone, (PTH); parathyroid hormone-related protein, (PTHrP); polyneuropathy, (PNP); pro-opiomelanocortin, (POMC); prostaglandins of the E series, (PGE); proteolysis-inducing factor, (PIF); small-cell lung cancer, (SCLC); syndrome of inappropriate antidiuretic hormone secretion, (SIADH); tissue factor, (TF); transforming growth factor alpha, (TGFα); tumor necrosis factor alpha, (TNFα); unfractionated heparin, (UFH); vascular endothelial growth factor, (VEGF); venous thromboembolism, (VTE); voltage-gated P/Q calcium channels, (VGCC)

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Summary

Paraneoplastic syndromes are frequently found in lung cancer. They can be the first manifestation of disease or recurrence. Neuromuscular, vascular, haematological and metabolic syndromes, as well as syndromes involving the connective and skeletal tissues and skin can be distinguished. While some of the paraneoplastic syndromes are commonly observed (eg. Anemia, cachexia) others are rare disorders (eg. Ospoclonus-myoclonus, tylosis). This review focuses on the epidemiology, pathogenesis, clinical symptoms and treatment options of frequent and clinical important paraneoplastic syndromes.

I. Introduction

Paraneoplastic syndromes are common in lung cancer, and may be the first manifestation of the disease or its recurrence (Bunn and Ridgway, 1993). Paraneoplastic phenomena are not related to the direct invasion, obstruction, or metastasis (Patel et al, 1993; Spiro, 1995). Neuromuscular, vascular, haematological and metabolic syndromes, as well as syndromes involving the connective and skeletal tissues and skin can be distinguished. Table I gives an overview of the paraneoplastic syndromes that have been described in lung cancer patients. In the following epidemiology, pathogenesis, clinical findings, and treatment options of the most common paraneoplastic syndromes in lung cancer will be reviewed.

II. Epidemiology

Paraneoplastic syndromes are estimated to occur in 7% to 15% of all patients with cancer (Richardson and Johnson, 1992). If the definition of paraneoplastic syndromes is broadened to include conditions such as anemia, cachexia, and hypercalcaemia then the incidence and prevalence of paraneoplastic syndromes is much higher. Lung cancer and small-cell lung cancer (SCLC) in particular is the most common cancer to be associated with paraneoplastic syndromes. However, some paraneoplastic syndromes are more often found in non-small-cell lung cancer (NSCLC). For example hypertrophic pulmonary osteoarthropathy has most often been described in association NSCLC.

The extent of paraneoplastic syndromes is unrelated to the size of the primary tumour. In some cases it may precede diagnosis of malignancy while in other cases it may occur late in the course of disease or may show up as the first symptom of recurrence. If lung cancer patients have paraneoplastic syndromes normally they suffer from only one syndrome. Literature data on multiple paraneoplastic syndromes in the same patient are sparse and are mostly described in case reports (Monsieur et al, 1995).
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### III. Hypercalcaemia

Hypercalcaemia is frequently found in patients with lung cancer. Its incidence ranges from 2 to 6% at presentation to 8 to 12% throughout the course of disease (Spiro et al, 2007). It may arise from bone metastasis but can also be induced in a paraneoplastic manner by secretion of parathyroid hormone-related protein (PTHRP), calcitriol or other cytokines, including osteoclast activating factors. Hiraki and colleagues examined 1149 patients with lung cancer and found 6% to have hypercalcaemia (Hiraki et al, 2004). Among those with hypercalcaemia 51% had squamous cell carcinoma, 22% had adenocarcinoma, and 15% had SCLC. Most of those patients had advanced disease (stage III or IV). Median survival was only 3.8 months (Hiraki et al, 2004).

Hypercalcaemia in lung cancer patients can be caused by either bony metastases or less commonly by paraneoplastic syndromes. Tumours can secrete PTHrP, calcitriol or other cytokines including osteoclast activating factors. Moseley and colleagues identified PTHrP expression in lung cancer cells (Moseley et al, 1987). PTHrP shares 70% sequence homology with PTH over the first 13 amino acids at the N-terminus. Both parathyroid hormone (PTH) and PTHrP bind to a common PTH/PTHrP receptor (Abou-Samra et al, 1992) and share similar biological activities (Horiuchi et al, 1987). However, expression of PTHrP has also been reported in normal tissue (Danks et al, 1989; Afa et al, 1990). This implicates that PTHrP has also a physiological effect. It is now clear that PTHrP has several other functions in addition to its PTH-like effects (Clines and Guise, 2005).

PTH stimulates osteoclastic bone resorption and calcium reabsorption and inhibition of phosphate reabsorption from renal tubules. It also stimulates renal 1α-hydroxylase resulting in production of 1,25-(OH)₂D₃, which increases intestinal absorption of calcium and phosphate. These actions result in increased serum calcium. PTH actions are mediated through binding of the amino terminus of the PTH molecule to the PTH receptor, a member of the family of G protein-coupled receptors that contain seven transmembrane-spanning domains (Jupner et al, 1991). The ligand-bound PTH receptor activates adenylate cyclase, through the activation of G protein Gas, producing cyclic adenosine monophosphate (cAMP) while activating protein kinase A. In addition, the phospholipase C/protein kinase C system also contributes to PTH signal transduction (Mahon et al, 2002; Swarthout et al, 2002).

Approximately 80% of cancer patients with hypercalcaemia have detectable or increased plasma concentrations of PTHrP (Burris et al, 1990). PTHrP has a multifunctional role in cancer. It mediates hypercalcaemia but also aids development and progression of osteolytic bone metastasis, regulates growth of cancer cells and acts as a cell survival factor (Luparello et al, 1993; Luparello et al, 1995; Li et al, 1996; Chen et al, 2002).

Although PTHrP is responsible for the majority of cases of paraneoplastic hypercalcaemia there have been rare cases with ectopic PTH production in the tumour. This has been reported in SCLC as well as in squamous...

While in haematological malignancies extra-renal production of 1,25-(OH)₂D₃ appears to be a major mediator of hypercalcaemia (Seymour et al, 1994) in lung cancer calciotriol does not seem to be the major mediator of PTH-like activity even if SCLC cell lines can synthesize 1,25-(OH)₂D₃ (Mawer et al, 1994).

Other factors that can stimulate osteocalcific bone resorption and cause hypercalcaemia include interleukin (IL)-1, IL-6, transforming growth factor alpha (TGFα), tumor necrosis factor alpha (TNFα), and granulocyte colony stimulating factor (G-CSF) (Cines and Guise, 2005). Human TGFα and TNFα stimulate osteocalcific bone resorption in vitro and result in hypercalcaemia in vivo (Bertolini et al, 1986; Yates et al, 1992; Ibbotson et al, 1995). Factors such as TGFα, IL-1, IL-6 and TNFα can also enhance the hypercalcaemic effects of PTHrP.

Although prostaglandins of the E series (PGE) are powerful stimulators of bone resorption (Klein and Raisz, 1970) there role in tumour-associated bone destruction remains unclear (Mundy, 1995). They may be mediators of cytokine effects on the bone. Moreover, PGE expression has been described in the lung cancer tissue of normocalcaemic patients (Kukrja et al, 1982). This finding implicates that PGE may not be necessary to induce hypercalcaemia in cancer patients.

Symptoms of hypercalcaemia include anorexia, nausea, vomiting, constipation, lethargy, polyuria, polydipsia, and dehydration. If untreated hypercalcaemia my lead eventually to confusion and coma. Renal failure and nephrocalcinosis are late manifestations, too. Symptomatic patients with a serum calcium of ≥ 3 mmol/L required treatment that includes hydration and biphosphonate (Thomas et al, 2004).

IV. Syndrome of inappropriate antidiuretic hormone secretion

Elevated levels of antidiuretic hormone (ADH) and impaired water handling can be observed in 30 to 70% of lung cancer patients (Patel et al, 1993). However, excess production of ADH does not always produce symptoms (Maurer et al, 1983; Bliss et al, 1990; Moses and Scheinman, 1991). Only 1 to 5% of all patients with lung cancer have symptoms attributable to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIDS is frequently caused by SCLC. In a study by List and co-workers approximately 10% of patients with SCLC had SIADH (List et al, 1986). In that study development of SIADH did not correlate with clinical stage or metastatic sites. SIADH occurred most often with initial presentation and promptly resolved with initiation of combined chemotherapy in 80% of the patients. Response to chemotherapy and survival was not influenced by the presence of SIADH (List et al, 1986). Recurrence of SIADH was associated with tumour progression.

Biochemically, the SIADH production is defined as low serum sodium and a dilute plasma osmolality along with a higher, or "inappropriate," urine osmolality, in the presence of continued urinary sodium excretion. A variety of hormones including atrial natriuretic peptide (ANP) have been implicated as possibly contributing to the hyponatremia found in lung cancer patients. However, only elevated plasma ADH levels were consistently found in patients with lung cancer and may explain the impaired ability to excrete the water load (Vorherr, 1974).

Physiologically ADH is released from the posterior pituitary gland whereas in paraneoplastic SIADH cancer cells secrete ADH (Moses and Scheinman, 1991). Another possible mechanism is inappropriate peripheral baroreceptor stimulation of ADH release from the hypothalamus (Vorherr, 1974). ADH causes hyponatremia and hypoosmolality that interfere with urinary dilution, thereby preventing the excretion of ingested water. An interesting observation in the SIADH is the development of partial escape from ADH which tends to protect against progressive water retention (Jaenike and Waterhouse, 1961). Although ADH secretion or effect is inappropriately increased in the SIADH, up to one-third of patients have a downward resetting of the osmostat in which the plasma sodium concentration is normally regulated (and therefore stable) at a new lower level, typically between 125 and 135 mmol/L. Establishing the presence of this condition is clinically important because correcting the hyponatremia is both unnecessary and likely to be ineffective, since raising the plasma osmolality will stimulate both ADH release and thirst.

Hyponatremia, plasma hypoosmolality and urine hyperosmolality with continuing sodium excretion are biochemical findings in SIADH. Water retention is typically only 2 to 3 liters and does not lead to edema or anasarca. The severity of symptoms in SIADH is related to the degree of hyponatremia and the rapidity of fall in serum sodium. Anorexia, nausea, and vomiting are common symptoms. A rapid onset of hyponatremia can cause cerebral edema. This may lead to irritability, restlessness, personality changes, confusion, coma, seizures, and respiratory arrest.

In patients with SCLC, SIADH resolves in up to 80% after administration of chemotherapy (List et al, 1986). Adjuvant management of SIADH includes fluid restriction to 800-1,000 ml/d to increase serum sodium. In patients with severe symptoms (severe confusion, convulsions, or coma) intravenous hypertonic saline (5%) solution (eg. 200-300 ml in 3-4 h) should be given.

V. Cushing syndrome

Adrenocorticotrophic hormone (ACTH) is the most commonly produced hormone in lung cancer patients. Increased levels of ACTH may be detectable in up to 50% of patients with lung cancer (Mendelsohn and Baylin, 1984). ACTH secretion is almost always associated with SCLC (Hansen, 1990). About 30% of all cases of SCLC are associated with hypersecretion of ACTH. However, a clinical apparent Cushing syndrome is rare (Menneckier et al, 1999). Cushing syndrome has been described in 1 to 5% of patients with SCLC (Odell et al, 1979; Ilias et al, 2005) but this may overestimate the real rate. In 2005 Hansen and Bork reported only 3 out of 90 cases of Cushing syndrome to be attributable to SCLC (Hansen and Bork, 1985). Most commonly, Cushing syndrome occurred in patients with pulmonary carcinoma (35 of 90...
patients). While ectopic ACTH syndrome typically presents as Cushing syndrome in patients with SCLC bronchial carcinoid tumors are the most common occult sources of ACTH (Terzolo et al., 2001).

SCLC associated with the ectopic ACTH syndrome is more resistant to chemotherapy and the severe hypercortisolism is responsible for a high rate oflife-threatening complications during treatment which worsens prognosis (Terzolo et al., 2001). Shepherd and colleagues retrospectively analyzed the charts of 545 patients with SCLC. They identified 23 patients (4.5%) with Cushing syndrome and ectopic ACTH production. These patients had a response rate to chemotherapy of only 46%, and their median survival was only 3.57 months (Shepherd et al., 1992).

In pituitary cells ACTH is derived by cleavage from the precursor, pro-opiomelanocortin (POMC). It is unlikely that processing of POMC is as efficient in non-pituitary cells. ACTH precursors and ACTH-related peptides can be secreted by POMC expressing cells. ACTH precursors can be detected in the serum of patients with ectopic ACTH syndrome (Oliver et al., 2003). Stewart and co-workers reported grossly elevated levels of ACTH precursors in patients with ectopic ACTH syndrome and increased concentrations of ACTH precursors in patients with SCLC without evidence of ectopic ACTH syndrome (Stewart et al., 1994).

SCLC cells have been shown to express POMC and secrete ACTH precursors (Stewart et al., 1989; White et al., 1989). POMC expression has also been observed in bronchial carcinoid tumour cells (Crosby et al., 1990). NSCLC is rarely associated with ectopic ACTH syndrome. In a case report of a patient with poorly differentiated squamous cell lung carcinoma and ectopic ACTH syndrome ACTH secretion of cancer cells was confirmed by immunohistochemical staining (Noorlander et al., 2006). Another case report described paraneoplastic Cushing syndrome in a patient with adenocarcinoma of the lung (Yoh et al., 2003).

ACTH and ACTH precursors stimulate the adrenal glands to secrete glucocorticosteroids. The symptoms and signs of paraneoplastic Cushing syndrome result directly from chronic exposure to excess glucocorticoid because of ectopic ACTH-production. There is a large spectrum of manifestations from subclinical to overt syndrome. Diagnosis is often difficult because there is no pathognomonic symptom. An important clinical hint to the presence of Cushing syndrome is the simultaneous development and increasing severity of several of the following symptoms: Centripetal obesity, facial plethora, glucose intolerance, weakness, proximal myopathy, hypertension, psychological changes, easy bruisability, hirsutism, oligomenorrhea or amenorrhea, impotence, acne, oily skin, abdominal striae, ankle edema, osteoporosis, polydipsia, polyuria, hyperpigmentation, headache, fungal infection specially oral thrush and hypokalimia.

To treat the paraneoplastic Cushing syndrome, treatment of the underlying disease is essential. In most cases treatment of the tumour will also improve the paraneoplastic syndrome. However, responses to chemotherapy in patients with SCLC and Cushing syndrome is only moderate (Shepherd et al., 1992). Severe symptoms should be treated symptomatically.

VI. Hematological abnormalities
Hematologic abnormalities including anemia, leukocytosis, thrombocytosis, and eosinophilia are frequently observed in lung cancer patients. Anemia is common in lung cancer patients. In one series 38% of untreated patients had a haemoglobin ≤ 12 g/dL. In contrast 80% of patients that were treated with chemotherapy were anaemic at one time (Kosmidis and Krzakowski, 2005). Leukocytosis is often found in patients with lung cancer either at time of diagnosis or during the course of the disease (Thomson et al., 1986). In one study leukocytosis had been described in 15% of all patients with lung cancer (n = 227). Nearly all patients had NSCLC. Leukocytosis was thought to be due to overproduction of granulocyte-colony stimulating factor (Kasuga et al., 2001). Tumor-related leukocytosis was associated with a poorer prognosis compared to patients without leukocytosis (median survival: 4.6 months vs 20.8 months) (Kasuga et al., 2001). Leukocytosis has also been associated with hypercalcemia (Kasuga et al., 2001; Hiraki et al., 2004). Thrombocytosis is observed in 16% to 32% of all lung cancer patients (Moller Pedersen and Milman, 1996; Aoe et al., 2004). It has been identified as an independent predictor of shorter survival (Moller Pedersen and Milman, 1996; Aoe et al., 2004). Eosinophilia in tissue or blood is rare. While tumour-associated tissue eosinophilia appear to have a better prognosis tumour-associated blood eosinophilia seem to be associated with a worse prognosis (Lowe, et al 1981).

The cause of anemia associated with cancer is multifactorial. Bleeding, hemolysis, bone marrow infiltration, and nutritional deficiencies may all contribute to the development of anemia in patients with cancer. In addition, inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IFN-γ, inhibit erythropoiesis, which leads to decreased production of erythrocytes, resulting in anemia. It has to be taken into account that anemia is a common complication of myelosuppressive chemotherapy (Groopman and Itri, 1999). On average, over one third of patients become anemic after three cycles of chemotherapy (Glasy et al., 2002).

Lung cancer has been shown to produce G-CSF which leads to leukocytosis (Asano et al., 1977). Granulocyte macrophage- colony stimulating factor (GM-CSF) and interleukin-6 production of lung carcinomas has also been reported to be associated with leukocytosis (Sawyers et al., 1992; Matsuguchi et al, 1991).

Anemia should be treated to improve quality of life. Erythropoiesis-stimulating agents such as epoetin and darbepoetin should be used with caution in cancer patients with anemia who are not receiving chemotherapy (Rizzo et al., 2008).

VII. Hypercoagulable disorders
A variety of hypercoagulable disorders including Trousseau’s syndrome (migratory superficial thrombophlebitis), deep venous thrombosis and
thromboembolism, disseminated intravascular coagulopathy, thrombotic microangiopathy, and nonthrombotic microangiopathy can be found in lung cancer. The incidence of venous thromboembolism (VTE) in lung cancer patients is around 40-100 cases per 1000 person-years compared to an estimated 1-2 cases per 1000 person-years in the general population (Tesselaar and Osanto, 2007). Chew and colleagues analyzed the data from 91,933 patients with newly diagnosed lung cancer and found that approximately 3% developed VTE within two years (Chew et al., 2008). Venous thromboembolism was associated with a higher risk of death within two years for NSCLC and SCLC. Lung cancer is one of the greatest purveyors of VTE (Girard et al., 2008).

Tumour cells can directly activate the clotting through two procoagulants: tissue factor (TF) and cancer procoagulant (CP) (Molnar et al., 2007). Human TF is the physiological initiator of blood coagulation. Goldin-Lang and co-workers found increased expression of full length human TF and alternatively spliced human tissue factor in NSCLC tissue compared to healthy controls (Goldin-Lang et al., 2008). Moreover, in that study expression of tissue factor was correlated with tumour stage and prognosis. Active TF-bearing microparticles, which may originate from the tumour cells themselves, have been found in the circulation of cancer patients. Microparticle-associated TF activity may provide a link between cancer and thrombosis and play a decisive role in the pathogenesis of the prothrombotic state in cancer patients (Tesselaar et al., 2007).

VTE in lung cancer should be treated the same as in non-cancer patients. Data from the literature suggest that low molecular weight heparin (LMWH) is likely to be superior to unfractionated heparin (UFH) in the initial treatment of VTE (Akl et al., 2008). For the long term treatment of VTE in cancer patients LMWH reduce VTE but not dead compared to oral anticoagulant therapy (Akl et al., 2008). In cancer patients without previous thrombotic incidents heparin has been shown to have a survival benefit especially in patients with limited SCLC (Akl et al., 2007). In contrast oral anticoagulation may not prolong survival. Only in patients with extensive SCLC a survival benefit of six months from warfarin is suggested according to the data from the literature (Akl et al., 2007).

VIII. Skeletal and collagen-vascular syndromes

Digital clubbing and hypertrophic pulmonary osteoarthropathy (HPO) is observed in approximately 12% of patients with adenocarcinoma of the lung and less frequently in other cell types (Stenseth et al., 1967). Inflammatory symptoms and pain may disappear with successful treatment of the tumour.

Dermatomyositis and polymyositis are associated with neoplasms in 40% of all cases. Besides ovarian cancer SCLC is the most frequent type of cancer (Hill et al., 2001). Gomm and colleagues studied 100 patients with lung cancer (35% had SCLC, 65% had NSCLC). In that study one patient presented with dermatomyositis and 33 patients had polymyopathie (Gomm et al., 1990).

The exact pathogenesis of digital clubbing and HPO is not known. In digital clubbing proliferation of connective tissue beneath the nail matrix is observed. Histochemical features of HPO include vascular hyperplasia, edema, and excessive fibroblast and osteoblast proliferation (Myers and Farquhar, 2001). In the past, neurogenic, hormonal, and vascular mechanisms have been discussed (Shneerson, 1981). More recently, the overexpression of vascular endothelial growth factor (VEGF) has been implicated as contributing to the pathogenesis of clubbing and HPO. Olsen and colleagues reported the case of a young woman with lung cancer and HPO. Serum levels of VEGF were elevated. After resection of the cancer VEGF levels fell and HPO remitted. Histochemical studies of the resected tumor showed increased VEGF messenger RNA expression, suggesting ectopic production by the lung cancer cells (Olan et al., 2004).

Dermatomyositis is characterized by infarcts, perifascicular atrophy, endothelial cell swelling and necrosis, vessel wall membrane attack complex deposition, and myocyte-specific MHC I upregulation in the muscle. Histopathological findings in the skin include hyperkeratosis, epidermal basal cell vacuolar degeneration and apoptosis, increased dermal mucin deposition, and a cell-poor interface dermatitis. The precise link between malignancy and inflammatory myopathy remains incompletely understood (Casciola-Rosen et al., 2005). Although dermatomyositis has been classically considered as humorally mediated disease newer evidence suggest that cell-mediated mechanisms and innate immune system dysfunction play a more important role in the pathogenesis (Krathen et al., 2008). Myositis-specific autoantigens are expressed at high levels in regenerating cell in myositic muscles and in several cancer cells (Levine, 2006). This may provide a link between cancer and paraneoplastic myositis syndromes.

Digital clubbing is an enlargement of the terminal segments of the fingers and/or toes due to proliferation of connective tissue beneath the nail matrix. HPO is a systemic disorder, which involves both a painful symmetrical arthropathy, usually of the ankles, wrists, and knees, and periosteal new bone formation in the distal long bones of the limbs.

Myositis is characterized by muscle weakness and muscle pain. Typically proximal muscles are involved. Dermatomyositis also shows characteristic cutaneous findings of heliotrope eruption, Gottron’s papules and a photodistributed eruption with poikiloderma. Raynaud phenomenon, interstitial lung disease and inflammatory arthritis can also be found.

Symptoms of HPO may resolve after tumour resection. If a patient is not operable the usual treatment includes nonsteroidal anti-inflammatory agents or a bisphophonate (Amital et al., 2004). The mainstay of therapy for dermatomyositis is corticosteroids (Iorizzo and Jorizzo, 2008).

IX. Neurologic syndromes

Paraneoplastic neurological syndromes are observed in only 0.01% of cancer patients chiefly those affected by
lungs, breast, ovarian or stomach cancer. However, these syndromes frequently cause major disability and limitation in patients’ daily activities (Mollina-Garrido et al., 2006). Neurologic syndromes in lung cancer include the Lambert-Eaton myasthenic syndrome (LEMS), limbic encephalopathy, polynuropathy (PNP), cerebellar degeneration, retinopathy, opsonclus-myoclonus, and autonomic neuropathy (Swash and Schwartz, 1990; Martina and Clay, 2005). Paraneoplastic neurologic syndromes may occur almost exclusively with SCLC. Incidence in lung cancer patients has been reported to range between 4 and 5% but may probably be lower (Swash and Schwartz, 1990). In a 1991 survey of 150 consecutive SCLC patients only two patients had LEMS (1%) and one patient suffered from PNP (<1%) (Elrington et al., 1991). In 2005 similar results were obtained in a study of 432 consecutive patients with SCLC (LEMS: 1.6%, PNP: <1%, subacute cerebellar degeneration: <1%, limbic encephalitis: <1%) (Seute et al., 2004).

In a study of 200 patients with paraneoplastic encephalomyelitis and anti-Hu antibodies pathologic or X-ray evidence of a tumour was obtained in 83%. Diagnosis of SCLC was made in 74% of those with histological diagnosis (Graus et al., 2001). The prognosis of patients with SCLC and paraneoplastic encephalomyelitis is poor (Spiegelman et al., 1989; Graus et al., 2001).

Opsonclus-myoclonus is a rare paraneoplastic neurologic disorder that is most often associated with SCLC (Anderson et al., 1988; Bataller et al., 2001). The presence of the anti-neuronal antibodies in the serum indicate a poor prognosis (Margery et al., 2003). In a study by Hassan and co-workers SCLC patients with opsonclus-myoclonus died within 3 months without treatment. In contrast, in that same study with appropriate chemotherapy about half of the patients reported improvement of neurologic symptoms and several became long-term survivors (6 to 84 months) (Hassan et al., 2008).

Autoimmune mechanisms seem to be responsible for the development of neurologic syndromes in cancer. Autoantibodies are commonly found in neurologic syndromes associated with cancer. Autoantibodies that are directed against ligand- or voltage-gated channels have been identified in several neuromuscular syndromes. These include antibodies against voltage-gated calcium channels (Lambert-Eaton syndrome), antibodies against voltage-gated potassium channel (acquired neuromyotonia), and antibodies against the neuronal AChR in autonomic ganglia (autoimmune autonomic ganglionopathy). There is good evidence that antibodies in these disorders cause changes in synaptic function or neuronal excitability by directly inhibiting ion channel function (Vernino, 2007).

In Lambert-Eaton syndrome antibodies against the presynaptic voltage-gated calcium channels can be found. This decreases calcium entry into the presynaptic terminal which prevents binding of vesicles to the presynaptic membrane and acetylcholine release (Mareska and Gutmann, 2004). Antibodies are most often directed against voltage-gated P/Q calcium channels (VGCC) but also antibodies against voltage-gated N calcium channels can be found (Lennon et al., 1995). Low titers of antibodies against the P/Q and the N type calcium channel were also found in approximately 30% of patients with paraneoplastic encephalomyeloneuropathic complications (Lennon et al., 1995).

Paraneoplastic encephalomyelitis is characterized by neuronal loss and inflammatory infiltrates in particular areas of the nervous system (Henson and Urich, 1982). It usually causes a severe neurological dysfunction, and antedates the diagnosis of SCLC in >70% of cases. In the majority of patients with paraneoplastic encephalomyelitis an antineuronal antibody, anti-Hu, can be found (Graus et al., 1985, 1986). This antibody recognizes a family of RNA-binding proteins (HuD, HuC, Hel-N1 and Hel-N2) expressed in the nuclei of neurones and SCLC cells (Szabo et al., 1991; King and Dropcho, 1996). Despite their crucial role in the development and maintenance of the neuronal phenotype the function of Hu antigens in the tumour cells is unknown. There is even no evidence that the anti-Hu antibodies are the cause of the neuronal damage (Sillevis Smitt et al., 1995; Carpentier et al., 1998). Nevertheless anti-Hu antibodies represent a useful diagnostic marker (Molinuevo et al., 1998). The antibodies probably are part of a more complex immune response against Hu antigens that is initially driven to control tumour growth but misdirected to cause neurological dysfunction (Posner and Dalmau, 1997).

At autopsy of patients with paraneoplastic neurologic syndromes lymphocytic infiltration is found in the areas of the central nervous system that correspond to neurologic deficits. This finding supports the hypothesis that autoantibodies play a key role in the pathogenesis of the neurologic syndromes.

Clinical features of paraneoplastic syndromes correspond to the underlying neurologic deficits. LEMS is characterized by muscle weakness with a predominance of the hip girdle. The motor weakness progresses in a cranio-caudal direction. Patients with limbic encephalopathy usually present with rapidly progressive short-term memory deficits, psychiatric symptoms, and seizures. Paraneoplastic PNP leads to distal symmetric sensorimotor deficits. Cerebellar degeneration is characterized by ataxia. Retinopathy leads to visual loss. Opsonclus is characterized by irregular, continual and conjugated chaotic saccades of the eyes. Opsonclus when accompanied by other symptoms of central nervous system involvement (head, appendicular myoclonus and truncal ataxia) constitutes the opsonclus-myoclonus syndrome. Paraneoplastic autonomic neuropathy is associated with a variety of symptoms including hypothermia, hyperventilation, sleep apnea, intestinal pseudo-obstruction, and cardiac arrhythmias.

Two general approaches have been tried to treat paraneoplastic neurologic syndromes based on the assumption that these syndromes are immune-mediated: removal of the antigen source by treatment of the tumour and suppression of the immune response. LEMS can be treated 3,4-diaminopyridine or intravenous immunoglobulin that have been shown to improve muscle strength. However, evidence from studies is limited (Maddison and Newsom-Davis, 2005). In patients with
underlying cancer chemotherapy has been successful (Verschuuren et al, 2006). For other paraneoplastic neurologic syndromes there is evidence that prompt oncologic treatment and immunotherapy (eg. Immunosuppression) can be beneficial (Keime-Guibert et al, 2000; Rosenfeld and Dalmau, 2003; Vernino et al, 2004).

X. Cutaneous syndromes

A variety of paraneoplastic cutaneous syndromes has been described in lung cancer patients (refer to Table 1). However, these syndromes are mostly non-specific and can be observed in both malignant and benign disease.

Palmo-plantar hyperkeratosis (PPH) also called tylosis is a rare paraneoplastic syndrome in lung cancer. In the literature it is mostly described in case reports (Schwindt et al, 1970; Nomori et al, 1996; Engin et al, 2002). It may typically precede the diagnosis of lung cancer for months or years (Burgdorf and Goltz, 1987). Prognosis of patients with lung cancer and PPH is poor (Nomori et al, 1996). Akanthosis nigricans has also been described in several case reports to be associated with adenocarcinoma, with squamous cell lung carcinoma or also with alveolar cell carcinoma (Horiiuchi et al, 1986; Menzies et al, 1988; Onai et al, 1989).

XI. Cachexia and fatigue

Cancer cachexia is perhaps the most common manifestation of advanced malignant disease (50%) and is responsible for approximately 25% of deaths from cancer (Leibach et al, 2007). The degree of cachexia is inversely correlated with survival time and always implies a poor prognosis.

Symptoms of cachexia include anorexia, weight loss, muscle loss, anemia, and alterations in carbohydrate, lipid and protein metabolism.

Cachexia is mainly driven by anorexia and metabolic alterations. Cancer patients frequently exhibit a relative glucose intolerance and insulin resistance. While significant loss of adipose tissue is observed in cancer cachexia lipolytic rates are not significantly increased. Lipogenesis seem to be reduced. Loss of skeletal muscle protein and decreased muscle protein synthesis is commonly observed in cachexia (Dworzak et al, 1998; Giordano et al, 2003). Changes in liver protein synthesis reflect aspects of the so-called acute-phase protein response. This is part of the general adaptation of the body often seen in trauma, inflammation, infection, and cancer. An acute-phase protein response can be observed in a significant proportion of patients with lung cancer. The presence of an acute-phase protein response has been related to accelerated weight loss in patients with lung cancer (Harvie et al, 2003).

A variety of mediators has been described to be involved in development of cachexia (Leibach et al, 2007). The tumour behaves like a new metabolically active organ. However, it is not clear whether the metabolic changes result from mediators released by the cancer or the host response (Argiles et al, 2003, 2008; Leibach et al, 2004). In general, serotonergic activity in the hypothalamus decreases appetite. In cancer patients increased levels of free tryptophan, a precursor of serotonin, are found (Brink et al, 2002). Amounts of tryptophan are closely related with reduced food intake. Changes in hormone levels and target-organ sensitivity have also been described in tumour patients. Elevated levels of cortisol and glucagons may amplify the acute-phase protein response in cancer patients (Schaub et al, 1979; Knapp et al, 1991). In addition, several proinflammatory cytokines including (TNF-α, IL-1, IL-6, interferon (IFN)-γ, and ciliary neutropic factor (CNTF) have been implicated in cachexia (Leibach et al, 2007). Apart from factors produced by the host tumour derived mediators have been described that may play an important role in the pathogenesis of cachexia. These mediators include proteolysis-inducing factor (PIF) and lipid mobilizing factor (LMF) (Cariuk et al, 1997; Hiraki et al, 1997).

At present therapy for cancer cachexia is difficult. Reversing malnutrition by traditional food intake is hampered by the protein-energy deficit and the associated wasting as well as the anorexia and the early satiety. Several drugs have been used to “repair” the altered metabolism. Corticosteroids are most widely used with a short benefit. Ibuprofen has been used with some effect due to its anti-inflammatory properties. Medroxyprogesteron acetate may improve appetite and stabilize weight. Eicosapentaenoic acid can lower the production of proinflammatory cytokines.

Cancer-related fatigue is also extremely common. Up to 90% of cancer patients report fatigue symptoms while in most studies prevalence rates are 60% (Cella et al, 2001). Fatigue is a highly subjective multidimensional experience. Individuals may perceive fatigue as physical tiredness or exhaustion, a need for reduced activity, reduced motivation, and/or mental fatigue (Ahlberg et al, 2003). Fatigue is experienced due to cancer and to treatment. The basic mechanisms of fatigue are broadly characterized into two main components: peripheral and central. Peripheral fatigue occurs in the neuromuscular junctions and muscle tissues. This results in the inability of the peripheral neuromuscular apparatus to perform a task in response to central stimulation. Central fatigue arises from the progressive failure to transmit motor neuron impulses. This leads to difficulties in the initiation or maintenance of voluntary activities (Chaudhuri and Behan, 2004; Romback and Hansson, 2004).

The etiology of fatigue is poorly understood. Several underlying mechanisms have been proposed based on studies in normal (exercise) conditions and in the context of chronic diseases, including chronic fatigue syndrome and rheumatoid arthritis (Ryan et al, 2007).

Several mechanisms have been shown to be involved in cancer-related fatigue. Studies in patients with chronic fatigue syndrome have demonstrated raised plasma levels of free tryptophan, which could potentially lead to high central serotonin levels (Castell et al, 1999; Badawy et al, 2005). An increase in brain serotonin (5-HT) levels and/or upregulation of a population of 5-HT receptors, may lead to reduced somatomotor drive, modified hypothalamic-pituitary-adrenal (HPA) axis function, and a sensation of reduced capacity to perform physical work (Andrews et al, 2004). Low levels of circulating cortisol have been
observed in patients with chronic fatigue syndrome (Cleare, 2003). Cancer, and/or cancer treatment may also alter the function of the HPA axis, resulting in endocrine changes that cause or contribute to fatigue. Cancer may cause fatigue by circadian rhythm disruption. Several alterations in circadian function have been demonstrated in patients with cancer. These include changes in endocrine rhythms (e.g., cortisol, melatonin, and prolactin secretion), metabolic processes (e.g., temperature and circulating protein levels), the immune system (e.g., levels of circulating leukocytes and neutrophils), and rest-activity patterns (Focan et al, 1986; Mormont and Levi, 1997; Vgontzas and Chrousos, 2002; Sephton and Spiegel, 2003; Levin et al, 2005). Cancer can lead to a defect in the mechanism for regenerating ATP in skeletal muscle can compromise the ability to perform mechanical tasks (Andrews et al, 2004). Reduced oxidative muscle metabolism, epiled cellular ATP associated with a dysregulated 2,5'-oligoadenylate synthetase/RNase L pathway, and impaired synthesis of ATP have been reported (McCully et al., 1996; Lane et al, 1998; Forsyth et al, 1999). Proinflammatory cytokines, such as TNF-α and IL-1β, are implicated in many of the mechanisms proposed for the etiology of fatigue associated with cancer and various illnesses (Konsman et al, 2002).

Treatment of cancer-related fatigue should be individualized according to the underlying pathology when a specific cause has been identified. In addition to older therapies, such as hematopoietics, antidepressants, corticosteroids, and psychostimulants, the new wake-promoting agent modafinil may offer an alternative therapeutic approach.

XII. Conclusions
Paraneoplastic syndromes are common in lung cancer patients. Some paraneoplastic syndromes can severely affect organ function and quality of life. Treating the underlying cancer is the first step. However, specific therapy may also be necessary.

References


