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TOPIC HIGHLIGHT

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Paraneoplastic syndromes associated with lung cancer

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Abstract

Paraneoplastic syndromes are signs or symptoms that occur as a result of organ or tissue damage at locations remote from the site of the primary tumor or metastases. Paraneoplastic syndromes associated with lung cancer can impair various organ functions and include neurologic, endocrine, dermatologic, rheumatologic, hematologic, and ophthalmological syndromes, as well as glomerulopathy and coagulopathy (Trousseau's syndrome). The histological type of lung cancer is generally dependent on the associated syndrome, the two most common of which are humoral hypercalcemia of malignancy in squamous cell carcinoma and the syndrome of inappropriate antidiuretic hormone secretion in small cell lung cancer. The symptoms often precede the diagnosis of the associated lung cancer, especially when the symptoms are neurologic or dermatologic. The proposed mechanisms of paraneoplastic processes include the aberrant release of humoral mediators, such as hormones and hormone-like peptides, cytokines, and antibodies. Treating the underlying cancer is generally the most effective therapy for paraneoplastic syndromes, and treatment soon after symptom onset appears to offer the best potential for symptom improvement. In this article, we review the diagnosis, potential mechanisms, and treatments of a wide variety of paraneoplastic syndromes associated with lung cancer.

Key words: Paraneoplastic syndrome; Small cell lung cancer; Non-small cell lung cancer; Symptom; Diagnosis; Treatment; Endocrine; Neurologic; Hematologic; Trousseau's syndrome

Core tip: A wide variety of paraneoplastic syndromes are associated with lung cancer, including endocrine, neurologic, dermatologic, rheumatologic, hematologic, and ophthalmological syndromes, as well as glomerulopathy and coagulopathy (Trousseau's syndrome). The histological type of lung cancer is generally dependent on the associated syndrome, the two most common of which are humoral hypercalcemia of malignancy in squamous cell carcinoma and the syndrome of inappropriate antidiuretic hormone secretion in small cell lung cancer. The symptoms of paraneoplastic syndromes often precede the diagnosis of lung cancer. The early detection and treatment of the underlying lung cancer offers the best outcomes for paraneoplastic syndromes.

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INTRODUCTION

Paraneoplastic syndromes are a group of clinical disorders that are associated with malignant diseases and are

Table 1 Criteria for the diagnosis of paraneoplastic endocrine syndromes

Abnormal endocrine function without physiologic feedback regulation
The absence of metastasis in the respective endocrine gland
Deterioration with increasing tumor burden
Improvement in endocrine function with the treatment of the tumor
Evidence of the presence of hormones in the tumor or hormone synthesis by the tumor

not directly related to the physical effects of the primary or metastatic tumors[1]. In the current understanding, these conditions arise from secretion of functional peptides or hormones from the tumor, or inappropriate immune cross-reaction between normal host cells and initially targeted tumor cells[2]. Although paraneoplastic syndromes can be associated with many types of malignancies, they are most frequently associated with lung cancer[3]. The histology of lung cancer influences the type of associated paraneoplastic syndrome. Paraneoplastic syndromes occur in approximately 10% of patients with lung cancer[1], and two of the most common are humoral hypercalcemia of malignancy (HHM) in squamous cell carcinoma and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in small cell lung cancer. There is no relation between the severity of symptoms and the size of the primary tumor, and in some cases, paraneoplastic syndromes are manifested before the diagnosis of cancer[1]. The early recognition of paraneoplastic syndromes may contribute to the detection of a highly treatable, early-stage tumor[2]. At other times, the syndromes may occur late in the course of disease or may appear as the first sign of recurrence[1]. Some syndromes, such as hypercalcemia and hematologic syndromes, are associated with a poor prognosis; others, such as onconeural antibody-related neurologic syndromes, may predict longer survival. This review provides an overview of a wide variety of paraneoplastic syndromes associated with lung cancer, with an emphasis on the diagnosis and treatment of the most frequently encountered syndromes. We searched the literature on PubMed (http://www.ncbi.nlm.nih.gov/pubmed) using the terms "lung cancer" and "paraneoplastic syndrome". As a result, we found more than 1000 studies published in the 21st century, and we cited these studies with priority. However, we also cited some older studies when only a few studies associated with the syndromes had been published in the 21st century.

PARANEOPLASTIC ENDOCRINE SYNDROMES

Lung cancers have a potential to synthesize and secrete peptides or hormones that lead to a variety of endocrine syndromes[4]. There are several criteria for diagnosing a paraneoplastic endocrine syndrome (Table 1)[4]. However, all of these criteria may not be satisfied in a given patient[4]. In particular, the presence of hormones in the tumor tissue is not always necessary for a clinical diagnosis. Several paraneoplastic endocrine syndromes have been reported (Table 2), and the three most common of which are HHM, SIADH, and ectopic Cushing's syndrome (ECS)[4].

Table 2 Paraneoplastic endocrine syndromes and causes of hypercalcemia associated with lung cancer

Paraneoplastic endocrine syndromes associated with lung cancer
Humoral hypercalcemia of malignancy
Syndrome of inappropriate antidiuretic hormone production
Cushing's syndrome
Hypoglycemia
Acromegaly
Carcinoid syndrome
Gynecomastia
Hyperthyroidism
Causes of hypercalcemia associated with lung cancer
Humoral hypercalcemia of malignancy
(1) Parathyroid hormone-related protein
(2) Parathyroid hormone
(3) 1,25-dihydroxyvitamin D
(4) Granulocyte colony-stimulating factor
Osteolytic activity at the sites of skeletal metastases

HHM

The incidence of hypercalcemia in patients with lung cancer ranges from 2%-6% at the initial diagnosis to 8%-12% throughout the course of the disease[1]. The most common type of cancer related to hypercalcemia is squamous cell carcinoma, in which higher incidences up to 23% has been reported[2,4]. The two major mechanisms of hypercalcemia in cancer patients are: (1) HHM; and (2) osteolytic activity at sites of skeletal metastasis (Table 2). HHM is considered a paraneoplastic syndrome and accounts for 46%-76% of hypercalcemia in lung cancers[5]. Although four mechanisms of HHM have been described, the majority of HHM cases are caused by the secretion of parathyroid hormone (PTH)-related protein (PTHrP) from the tumor. Rare cases of HHM with ectopic PTH secretion by lung cancers have also been reported[6-8]. Although ectopic 1,25-dihydroxyvitamin D secretion is frequently observed in patients with malignant lymphoma[5], no cases of 1,25-dihydroxyvitamin D-producing lung cancer have been reported, to our knowledge. Another mechanism of HHM may be mediated by granulocyte colony-stimulating factor (G-CSF)[9,10]. Long-term exposure to G-CSF results in the stimulation of osteoclastic bone resorption or an increase in osteoclast progenitors[9,10].

The PTHrP has significant homology with PTH in the amino-terminal region[11], and both PTH and PTHrP bind to a common PTH/PTHrP receptor[12]. PTHrP and PTH exert equivalent actions in regulating bone resorption and renal calcium/phosphorus levels[5]. However, unlike PTH, PTHrP does not increase 1-hydroxylase activity and 1,25-dihydroxyvitamin D production[5]. In two lung squamous cell carcinoma xenograft models of hypercalcemia, the inhibition of autocrine epidermal

Table 3 Syndrome of inappropriate antidiuretic hormone secretion

Hyponatremia (serum sodium < 134 mEq/L)
Hypoosmolality (plasma osmolality < 275 mOsm/kg)
Inappropriately high urine osmolality (> 500 mOsm/kg)
Inappropriately high urinary sodium concentration (> 20 mEq/L)
Absence of hypothyroidism
Absence of adrenal insufficiency
Absence of volume depletion

growth factor receptor (EGFR) signaling has been shown to reduce plasma PTHrP and total calcium concentrations[13]. Amphiregulin stimulation of EGFR resulted in high levels of PTHrP gene expression in squamous cell carcinomas[14]. Furthermore, the reconstitution of the amphiregulin-EGFR signaling system in a squamous cell carcinoma line led to HHM and rapid osteolytic growth in animal models[14].

HHM is usually found in patients with an increased tumor burden[4], and therefore, the incidence increases late in the course of illness. A very poor prognosis has been reported in patients with hypercalcemia, with a median survival of 1-3 mo[9,15]. The clinical features of hypercalcemia include circulatory effects (thirst, polyuria, dehydration, and renal failure), gastrointestinal effects (anorexia, nausea, vomiting, abdominal pain, and constipation), neurologic effects (fatigue, muscular weakness, confusion, lethargy, irritability, and coma), and psychiatric manifestations (depression, anxiety, and cognitive dysfunction)[1,2,4,5]. The severity of the symptoms are influenced by the patient's baseline renal functions, neurologic conditions, and the rapidity of progression of hypercalcemia as well as the degree of hypercalcemia[2,5,16]. Pancreatitis due to hypercalcemia is a less common but serious complication[17].

In the absence of ionized calcium measurements, total calcium, which represents both bound and unbound calcium, should be corrected for the albumin concentration using the following formula: corrected Ca (mg/dL) = measured Ca (mg/dL) + [0.8 × (4.0 - albumin (mg/dL)][2]. It is important to measure the calcium and albumin concentrations at the same time because the albumin concentration is often lower than 4.0 mg/dL in patients with cancer. In addition, including the constant 0.8 in the calculation is important to avoid the overestimation of hypercalcemia when the serum albumin level is very low.

Although the optimal approach to paraneoplastic hypercalcemia is to treat the underlying tumor[2], fluid replenishment with normal saline should be the initial treatment. This replenishment corrects the dehydration, increases the glomerular filtration rate, and also decreases renal calcium reabsorption[2]. Loop diuretics should not be routinely used for all patients with hypercalcemia although these agents inhibit renal calcium reabsorption. However, these agents may be added after adequate fluid replenishment in order not to deteriorate the dehydration and hypercalcemia[2,16]. Bisphosphonates such as zoledronate and pamidronate have been widely used because of their inhibitory effect of bone resorption mediated by osteoclasts and less toxicity[2]. The calcium levels in serum generally decrease within 2-4 d and reach a nadir 4-7 d after intravenous bisphosphonate administration, and the favorable efficacy usually continues for up to 3 wk[2,16]. The time to achieve normocalcemia is positively correlated with the pretreatment level of PTHrP[18]. The main adverse effects of bisphosphonates are renal dysfunction and osteonecrosis of the jaw[2]. Osteonecrosis of the jaw is caused by reduced local blood flow and leads to pain, swelling, loosened teeth, and exposed bone[2]. Calcitonin is a useful adjunctive initial therapy that inhibits bone resorption and increases the renal excretion of calcium[4,5]. The efficacy of calcitonin appears rapidly, but the effect is often partial and temporary[4,19]. Denosumab, a receptor activator of nuclear factor-kappa B ligand-targeted monoclonal antibody, was superior to zoledronic acid in delaying or preventing skeletal-related events in patients with bone metastases and was generally well tolerated[20]. The efficacy of denosumab for treating HHM is currently being evaluated in a phase II clinical trial[5].

SIADH

SIADH manifests as euvolemic hypoosmolar hyponatremia characterized by low serum osmolality and inappropriately high urine osmolality in the absence of diuretic treatment, adrenal insufficiency, heart failure, cirrhosis, or hypothyroidism (Table 3)[21]. Clinical SIADH has been reported to occur in 7%-16% of SCLC cases[22-24]. Approximately 70% of paraneoplastic SIADH cases are associated with SCLC[25]. Non-small cell lung cancer (NSCLC) has also been reported as a rare cause of SIADH[26-28]. The stage of SCLC is not related to the incidence of SIADH[22,23]. Patients with SCLC with hyponatremia had shorter survival times than patients with normal serum sodium levels[29,30]. In a study of 61 patients receiving two or more cycles of chemotherapy, the patients who did not fully regain normal serum sodium levels had poorer survival compared with the patients who did[30].

Non-ADH-mediated causes of hyponatremia, including insufficient intake of sodium, sodium wasting because of drug nephrotoxicity, and infusion of hypotonic fluid, should be distinguished from SIADH in the differential diagnosis of hyponatremia[21]. Paraneoplastic hyponatremia secondary to elevated atrial natriuretic peptide (ANP) has also been reported[31]. Most SCLC cell lines have been shown to produce ANP[32,33]. Of the 23 SCLC lines examined, 16 (70%) had elevated ANP levels[33], whereas only two (8.7%) had elevated ADH levels, and these two also had elevated ANP levels[33]. Of 11 cell lines derived from SCLC patients with hyponatremia, 9 produced ANP mRNA, 7 produced ADH mRNA, and 5 produced both ANP and ADH mRNAs[29]. Other studies have found that the plasma levels of ANP were also elevated in SIADH[34-37]. In addition, when hyponatremia was corrected *via* water restriction or demeclocycline administration, the plasma ANP levels decreased significantly into

the normal range[35].

The symptoms of SIADH are affected by the development speed and the degree of hyponatremia[2]. Headache, general fatigue, muscle weakness, and memory loss are common symptoms. Serum sodium levels less than 125 mEq/L, particularly if they develop within 48 h of hyponatremia onset, can lead to the alterations of mental and emotional status, loss of consciousness, seizures, and in some cases, even death[2,38]. On the other hand, when hyponatremia develops slowly, neurologic complications are less likely to occur[2,39].

The most effective long-term therapy for SIADH associated with SCLC is the treatment of the tumor itself[4,22,23]. Chemotherapy for SCLC results in the improvement of more than 80% of cases of clinically manifested SIADH[4,22,23]. However, with SCLC recurrence, 60%-70% of patients will experience a recurrence of SIADH as well[4]. Rarely, chemotherapy-induced tumor lysis may be associated with the sudden onset of SIADH[40]. In addition to the therapy directed to SCLC, other treatments are also required to normalize serum sodium levels. There are no evidence-based guidelines for managing SIADH[21]; the recommended management is based on expert opinion[21,39,41]. Free water restriction (< 1 L/d) is the first-line treatment for mild, asymptomatic SIADH. Adequate sodium intake, if necessary by thesalt tablets, also contribute to correcting hyponatremia. In life-threatening or acute cases of severe (< 120 mEq/L), symptomatic hyponatremia, a hypertonic 3% saline infusion is administered at a rate of approximately 1 mL/kg per hour for the first several hours. In SIADH, the urine osmolality is often higher than that of normal saline (308 mOsm/kg), and in these cases, administration of normal saline will lead to the increase in volume of free water, which results in further deterioration of hyponatremia[2]. Demeclocycline, an antibiotic in the tetracycline group, has been demonstrated to be effective in treating SIADH[4,42]. Demeclocycline decreases the renal response to ADH, resulting in a dose-dependent and reversible decrease in the urine-concentrating ability of the kidney. Vasopressin (ADH) receptor antagonists, such as conivaptan, an intravenously administered agent, and tolvaptan, an oral agent, are also available for the treatment of SIADH[2,43,44]. In the renal collecting ducts, these antagonists can block ADH to bind to the receptors, resulting in the urinary free water excretion rate[39]. Although high sensitivity to tolvaptan in SIADH has been reported[45], the United States Food and Drug Administration (FDA) announced restrictions on the use of tolvaptan in 2013 because of the risk of serious and potentially fatal liver injury. Other adverse effects of vasopressin receptor antagonists include nausea, vomiting, diarrhea, and infusion site reaction[2]. These agents are usually administered only in the cases of the fluid restriction failure[2]. When possible, medications that exacerbate SIADH, such as opioids, certain antidepressants, vinca alkaloids, and cisplatin, should be discontinued[46].

ECS

The manifestations of ECS are due to hypercortisolism, which generally resulted from the uncontrolled secretion of adrenocorticotropic hormone (ACTH) from nonpituitary tissue[4,21]. ECS represents approximately 12% of all patients with CS[47]. ECS caused by the production of corticotropin-releasing hormone (CRH) is rare, and only a few patients with ECS and SCLC have been reported[48,49]. Approximately 50% of ECS cases are neuroendocrine lung tumors; carcinoid tumors and SCLC constitute 36%-46% and 8%-20% of ECS cases, respectively[50-52]. ECS is clinically apparent in 1.6%-4.5% of SCLC cases[53,54], although immunoreactive ACTH was found in almost all tissue extracts of lung cancer from patients without clinical evidence of CS[55]. Rarely, ECS cases from NSCLC have also been reported[56].

The clinical features of ECS include moon face, acne, purple striae, proximal muscle weakness, peripheral edema, hypertension, and metabolic alkalosis with hypokalemia[21]. Almost all ECS patients show hypokalemia, and in the majority, hyperglycemia is observed[53,54,57]. However, ECS secondary to SCLC rarely exhibits all of the classic signs of CS[58]. One reason for this finding could be the brief duration of exposure to excessive ACTH due to the aggressive nature of SCLC[4]. The poor prognosis of patients with ECS has been reported compared with that of patients without ECS[57,59].

If the clinical features of CS are present in a patient with lung cancer, iatrogenic causes of CS, such as exogenous glucocorticoid use, must be excluded[21]. The clinical practice guidelines of the Endocrine Society recommend the initial use of one of the following first-line tests with high diagnostic accuracy, based on the suitability for a given patient: (1) at least two measurements of 24-h urinary free cortisol (greater than the normal range); (2) two measurements of late-night salivary cortisol (at bedtime or between 23:00 and 00:00, greater than 145 ng/dL); and (3) the 1-mg overnight dexamethasone suppression test (the administration of dexamethasone at 23:00 or 00:00 combined with blood cortisol measurements at 08:00 or 09:00 revealing a concentration greater than 1.8 μg/dL) or, in certain populations, the 2-mg 48-h dexamethasone suppression test[60,61]. If one of these tests produces abnormal results, further evaluation by an endocrinologist is recommended and should include one of the above tests or, in some cases, a serum midnight cortisol or dexamethasone-CRH test[61]. For the high-dose (8 mg) dexamethasone test, urinary or serum cortisol suppression greater than 50% is considered indicative of Cushing's disease with a sensitivity of 84%-89%[62-65]. Based on the high-dose dexamethasone test, 6%-31% of ECS patients also exhibit the suppression of serum or urinary cortisol or 17-OHCS[65-67]. Computed tomography (CT) scanning is useful for identifying ectopic sources of cortisol. Although ^{111}In-octreotide scintigraphy (Octreoscan) generally does not reveal a source that is undetectable on CT, it can provide supportive functional data[68,69].

The ideal treatment for ECS is the radical excision of the tumor[68]. In addition to the treatment of the underlying lung cancer, the direct inhibition of cortisol secretion is the considerable treatment for ECS[2]. Ketoconazole, metyrapone, etomidate, mitotane, and mifepristone can be used to reduce circulating glucocorticoids[21]. Among these agents, ketoconazole might have the best tolerance in spite of having some toxicity such as nausea and liver injury[2,70]. An additional option is octreotide, which blocks the release of ACTH, although it is not universally effective[4,71,72]. When these medications have unsuccessful result, bilateral adrenalectomy might be considered[4].

The prognosis of patients with ECS is influenced by tumor histology and by the severity of hypercorticolemia because both factors affect mortality and morbidity[68]. Most patients with ECS due to SCLC present at an advanced stage and have a poor response to chemotherapy[1,4].

Hypoglycemia

Tumor-associated hypoglycemia is rare and insulin-producing islet cell tumor is the best known cause. Nonpancreatic tumors may also cause recurrent hypoglycemia, known as non-islet cell tumor hypoglycemia (NICTH). NICTH is usually caused by the production of insulin-like growth factor (IGF)-2 from the tumor cells[2]. NICTH is suspected when low levels of serum insulin (usually < 1.44 IU/mL) and C-peptide (usually < 0.3 ng/mL) in addition to low levels of blood glucose with acute episodes. Moreover, the characterization of NICTH includes low levels of growth hormone (GH) and IGF-1 and normal or elevated levels of IGF-2[2]. The IGF-2 produced by nonpancreatic tumors is usually incompletely processed or unprocessed, referred to as "big" IGF-2 because its molecular weight is 10-17 kDa, in contrast to mature IGF-2, which has a molecular weight of 7.5 kDa[73]. Big IGF-2 impairs the formation of the heterotrimeric, 150 kDa IGF-binding protein (IGFBP) complex, which consists of IGF-1, IGF-2, IGFBP-3, and an acid-labile subunit[73,74]. In normal individuals, most circulating IGF is bound to this complex and is prevented from displaying its insulin-like potential[73]. When the formation of the 150-kDa complex is impaired, IGF is sequestered in a binary complex with IGFBP-3[73,75]. In the latter complex, the bioavailability of IGF is increased and its insulin-like potential is unmasked, leading to hypoglycemia[73,75]. Rarer cases of NICTH of the lung due to the production of insulin or IGF-1 have also been reported[73,76].

The treatment of the underlying tumor is the optimal approach to NICTH[2]. However, the first-line treatment should be the maintenance of adequate blood glucose levels. In the acute situation, parenteral dextrose administration is usually performed although oral intake can also be considered if possible. Intravenous administration of one 50 mL ampule of 50% dextrose fluid results in a rapid elevation in blood glucose levels[2]. Chronic and/or recurrent hypoglycemic episodes have also been observed in NICTH, and continuous infusion or oral intake of dextrose may be necessary. Other longer-term management includes glucagon, GH, or corticosteroids[73,74,77,78].

Acromegaly

In the vast majority of cases, acromegaly is caused by a pituitary adenoma. Ectopic acromegaly is rare (< 1% of cases) and is usually caused by ectopic growth hormone-releasing hormone (GHRH) or, less frequently, by ectopic GH secretion from the tumors[79,80]. The most common tumors that secrete ectopic GHRH or GH are bronchial carcinoids and pancreatic islet cell tumors[79,81]. Other types of lung cancer associated with acromegaly have also been reported, including SCLC, bronchioloalveolar carcinoma, and epidermoid carcinoma[82-84]. In some cases, IGF-I might play a role in the development of acromegaly[83,85].

The routine evaluation of circulating GHRH in acromegalic patients may enable the early recognition of overproduction of GHRH because plasma levels greater than 0.3 ng/mL are virtually diagnostic of a GHRH-producing tumor[79]. In contrast, the dynamics of ectopic GH secretion in ectopic acromegaly are characterized by high basal GH levels, which are not suppressed by glucose load, and by low or undetectable plasma GHRH levels[80].

Complete surgical resection of the tumor is the best treatment for ectopic acromegaly, and it usually leads to the normalization of GH levels and the regression of acromegalic features[80,86,87]. Residual, recurrent, and inoperable lesions have been successfully treated with octreotide and other somatostatin analogs[88-91].

PARANEOPLASTIC NEUROLOGICAL SYNDROMES

Paraneoplastic neurological syndromes (PNSs) are neurological disorders caused by the remote effects of cancer and are not caused by the tumor itself, its metastasis, infection, ischemia, or metabolic disruption[92]. In response to the development of a tumor, some antibodies against the tumor can be generated, that are known as onconeural antibodies[2]. These onconeural antibodies and the associated onconeural antigen-specific T lymphocytes inadvertently attack both the components of the nervous system and tumor cells[2]. Fewer than 50% of patients with PNS harbor known antibodies although many types of antibodies have been reported[92]. Therefore, the absence of known antibodies does not rule out a diagnosis of PNS[92]. In 80% of cases, the neurological disorder develops before the cancer becomes clinically overt, and the patient is referred to a neurologist for the identification of a neurological disorder as paraneoplastic[92].

In 2004, an international panel of neurologists advocated two levels of evidence for the diagnosis of a PNS: "definite" and "possible"[93]. They defined "classical" syndromes and "well-characterized" onconeural antibodies,

Table 4 Classical and non-classical paraneoplastic neurological syndromes[93]

Syndromes of the central nervous system
Encephalomyelitis[1]
Limbic encephalitis[1]
Brainstem encephalitis
Subacute cerebellar degeneration[1]
Opsoclonus-myoclonus[1]
Optic neuritis
Cancer-associated retinopathy
Melanoma-associated retinopathy
Stiff person syndrome
Necrotizing myelopathy
Motor neuron diseases
Syndromes of the peripheral nervous system
Subacute sensory neuropathy[1]
Acute sensorimotor neuropathy
Guillain-Barre syndrome
Brachial neuritis
Subacute/chronic sensorimotor neuropathies
Neuropathy and paraproteinaemia
Neuropathy with vasculitis
Autonomic neuropathies
Chronic gastrointestinal pseudo-obstruction[1]
Acute pandysautonomia
Syndromes of the neuromuscular junction and muscle
Myasthenia gravis
Lambert-Eaton myasthenic syndrome[1]
Acquired neuromyotonia
Dermatomyositis[1]
Acute necrotizing myopathy

[1]Classical syndromes.

Table 5 Onconeural antibodies

Well-characterized onconeural antibodies
Anti-Hu (ANNA1)
Anti-Yo (PCA1)
Anti-CV2 (CRMP5)
Anti-Ri (ANNA2)
Anti-Ma2 (Ta)
Anti-amphiphysin
Partially characterized onconeural antibodies
Anti-Tr (PCA-Tr)
ANNA3
PCA2
Anti-Zic4
Anti-mGluR1
Other antibodies
Anti-acetylcholine receptor
Anti-nicotinic AchR
Anti-voltage-gated calcium channel
Anti-voltage-gated potassium channel
Anti-NR1/NR2 of N-methyl-D-aspartate
Anti-glutamic acid decarboxylase

ANNA: Anti-neuronal nuclear antibodies.

and determined each level by combining the criteria with the evidence of cancer status (presence or absence)[93]. PNS can affect the central nervous system (CNS), the peripheral nervous system, and the neuromuscular junction and muscles. The classical and non-classical syndromes identified by the panel are shown in Table 4. It should be noted that these syndromes are also seen in non-paraneoplastic[2]. Particularly, more than 70% of patients with subacute sensory neuropathy and limbic encephalitis (LE) are not associated with cancer[92]. Well-characterized and partially characterized onconeural antibodies determined by the panel are shown (Table 5). A study of 200 patients with SCLC reported prevalence rates of onconeural antibodies for Hu, CRMP5, amphiphysin, Yo, Ri, and Ma2 of 22.5%, 5.0%, 2.5%, 0.5%, 1.5%, and 1%, respectively[94]. These antibodies may be detected in individuals without neurologic symptoms[2,93]. In particular, a high frequency of anti-Hu antibody has been reported, including 16% of 196 SCLC patients without PNS in one study[93]. In this regard, anti-Hu antibody titers may be important because none of the 109 SCLC patients without PNS had high titers of anti-Hu, whereas 44% of 57 patients with PNS had high titers (> 1:10000). Antibodies that occur in both cancer- and non-cancer-associated syndromes were not defined as onconeural antibodies, which include anti-acetylcholine receptor (AchR), anti-nicotinic AchR, anti-voltage-gated calcium channel (VGCC), anti-voltage-gated potassium channel (VGKC), anti-NR1/NR2 subunits of the N-methyl-D-aspartate (NMDA) receptor, and anti-glutamic acid decarboxylase (GAD) antibodies[2,93,95]. The diagnostic criteria for PNS described by the panel are presented in Table 6. When cancer and a classical syndrome develop, the diagnosis of a PNS can be made without the presence of onconeural antibodies. The time period of five years determined in the criteria was based on previous work demonstrating that cancers almost always developed in five years after the occurrence of neurological symptoms[93]. Importantly, even in the absence of a detected cancer, a neurological syndrome accompanied by the presence of well-characterized onconeural antibodies leads to the diagnosis of definite PNS. However, false-positive cases can exist in this set of criteria, in which cancer will never develop, although a very small number of cases are applicable[93]. The most plausible explanation is the elimination of cancer mediated by the host immune systems[96]. The panel emphasized that in cases of both definite and possible PNS, all other causes that might lead to the neurological symptoms should be excluded on the diagnosis of a PNS, even if onconeural antibodies are detected[93]. In fact, neurological alterations arise from many conditions other than PNS in the patients with cancer: brain metastasis, leptomeningeal disorders, nerve root or spinal cord invasion or compression, uncontrolled electrolytes and blood glucose, and adverse effects due to treatments such as irradiation and cytotoxic agents, including vinca alkaloidsm taxanes, and platinums[2]. Opioids such as morphine, phentanyl, and oxycodone, which are often administered during cancer treatment, can also cause neurologic and psychiatric changes.

Although PNSs are rare and occur in fewer than 1% of cancer patients overall, up to 3%-5% of patients with SCLC develop PNSs[95,97]. The irreversible destruction of neurons and nervous systems by the inflammation con-

tributes to the severity in most PNSs[92,98,99]. PNSs are usually progressive, and they debilitate patients deeply within weeks to months in many cases[92]. In general, a paraneoplastic case is highly suspected when symptoms are progressive in a subacute course and disability remains severe[92]. SCLC accounts for more than 90% of cases of PNS that are positive for anti-Hu antibody [also known as type 1 anti-neuronal nuclear antibodies (ANNA1)][1]. The Hu antigen is normally found in neurons. However, healthy adults do not have anti-Hu antibodies because the developing CNS is sequestered from the immune system by the blood-brain barrier[1]. Most SCLCs express the Hu antigen, and approximately 20% of patients with SCLC have detectable levels of circulating anti-Hu antibodies, although PNS will not develop in all of these patients[1,96]. Because many types of PNS are associated with anti-Hu antibody, the term "anti-Hu syndrome" has been used as an independent entity[21]. The clinical manifestations of anti-Hu syndrome may include encephalomyelitis, LE, brainstem encephalitis, cerebellar degeneration, opsoclonus-myoclonus, sensory neuropathy, and chronic gastrointestinal pseudo-obstruction (CGP)[21,93]. In several patients with anti-Hu antibody-positive SCLC, the spontaneous regression of SCLC without treatment has been reported, suggesting a host immune response directed against both cancer and the nervous system[100-102]. T and natural killer (NK) cell-mediated autoimmunity may play a role in the pathogenesis of the neurologic damage caused by SCLC[21,103-105].

Successful treatment of SCLC favorably affects the course of PNS[106]. Limited experience suggests that immunosuppressive therapy with a combination of IV immunoglobulin (IVIg), methylprednisolone, and cyclophosphamide may transiently stabilize the PNS; however, these treatments cannot improve PNS over the long term[98].

Encephalomyelitis

In response to the obstacle of various levels of the CNS, patients with encephalomyelitis exhibit relevant clinical dysfunction[93]. The terms "encephalomyeloneuritis" and "encephalo neuropathy" have also been used to describe this entity[93]. The main clinical syndromes observed in encephalomyelitis vary and include the following: subacute cerebellar degeneration, myelitis, LE, brainstem encephalitis, and even several peripheral nervous system dysfunction such as subacute sensory neuropathy[93]. However, if the clinical signs and symptoms are elucidative by a single level dysfunction of the CNS, the term "encephalomyelitis" should not be used, and the above described syndromes should be chosen according to the prominent symptoms[93].

LE

LE is clinically suspected with the acute or subacute progression, over the period of several days to three months, and symptoms including personality changes, irritability, depression, seizures, memory loss, confusion, and sometimes dementia[93,107]. Twenty percent of LE cases are associated with neoplasms[92]. In a study of 50 paraneoplastic LE patients, 50% had lung cancer, including 40% of the SCLC patients and 10% of the NSCLC patients[107]. Anti-Hu antibody is present in 36-50% of patients with paraneoplastic LE[107,108]. Anti-Ma2 antibody (Ta) was detected in 20% of patients with paraneoplastic LE, typically those with testicular cancer[107]. Anti-CRMP5 (CV2) and anti-amphiphysin antibodies have been reported less frequently[95]. The presence of anti-VGKC antibodies has been reported in idiopathic and paraneoplastic LE[109,110]. The electroencephalographic findings include focal or generalized slow activity, and epileptic activity in the temporal lobes[111]. The magnetic resonance imaging (MRI) findings reveal high signal intensities in unilateral or bilateral temporal lobes in 70%-80% of the patients using with T2 emphasized or fluid-attenuated inversion recovery (FLAIR) image[107,111]. CSF analysis has been reported to show evidence of inflammation, including pleocytosis, elevated protein, elevated IgG, and oligoclonal bands, in 80% of LE patients and may support the clinical diagnosis[93,107]. CSF analysis is also important to exclude carcinomatous meningitis.

Unlike most paraneoplastic syndromes of the CNS, paraneoplastic LE is well known for its favorable response to therapy[112]. Therapy for underlying SCLC is the best treatment for paraneoplastic LE, although immunosuppressive therapy is sometimes encouraged for paraneoplastic LE. The treatment of the tumor was found to improve the neurological syndrome in 73% of patients[107]. Chemotherapy improved neurologic symptoms accompanied by regression of the tumor[113] or the resolution of the temporal lobe signal abnormalities[114].

Subacute cerebellar degeneration

This syndrome has often been described using other terms, such as paraneoplastic cerebellar degeneration (PCD) or cerebellar ataxia[2,92]. To define subacute cerebellar degeneration (SCD), the following criteria are required: no evidence of significant cerebellar atrophy more than the expected on MRI, subacute development of the symptoms within three months, and a severity of at least 3 (moderate disability; requires some help) on the Rankin scale[93]. Approximately 50% of SCD cases have a paneoplastic origin[92].

Purkinje cells represent one of the most common targets of the immune response in patients with cancer, and the death of Purkinje cells results in SCD[95]. In an analysis of 50 patients with antibody-associated SCD, the following antibodies were detected: anti-Yo (19 patients), anti-Hu (16 patients), anti-Tr (7 patients), anti-Ri (6 patients), and anti-mGluR1 (2 patients)[115]. In contrast to limbic encephalitis, the frequency of the anti-Hu antibody in cerebellar degeneration is low (18%-31%)[115-117]. The underlying tumor is associated with the types of antibodies present: gynecological and breast cancers are associated with anti-Yo and anti-Ri, lung cancer with anti-Hu, and Hodgkin's lymphoma with anti-Tr and anti-

Table 6 Criteria for the diagnosis of paraneoplastic neurological syndromes[93]

Definite PNS
A classical syndrome and cancer that develops within five years of the diagnosis of the neurological disorder
A non-classical syndrome that resolves or improves significantly after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission
A non-classical syndrome with onconeural antibodies (well characterized or not) and cancer that develops within five years of the diagnosis of the neurological disorder
A neurological syndrome (classical or not) with well-characterized onconeural antibodies and no cancer
Possible PNS
A classical syndrome, no onconeural antibodies, and no cancer, but a high risk of an underlying tumor
A neurological syndrome (classical or not) with partially characterized onconeural antibodies and no cancer
A non-classical syndrome, no onconeural antibodies, and cancer present within five years of the diagnosis

PNS: Paraneoplastic neurological syndromes.

Table 7 Criteria for the diagnosis of Lambert-Eaton myasthenic syndrome

Clinical features
(1) Proximal muscle weakness
(2) Autonomic symptoms
(3) Reduced tendon reflexes
Anti-voltage-gated calcium channel antibodies
Repetitive nerve stimulation abnormalities
(1) Low compound muscle action potential
(2) Decrease > 10% at low frequency (1-5 Hz)
(3) Increase > 100% after maximum voluntary contraction or at high frequency (50 Hz)

mGluR1[115]. In fact, 14 (88%) of 16 anti-Hu-positive SCD patients had lung cancer[115]. Lung cancers associated with anti-Ri[118] or anti-Tr[119] have also been reported, with the most common being SCLC, although NSCLC has also been reported[119-121]. It has been reported that P/Q-type VGCC antibodies, which are thought to be associated with the development of Lambert-Eaton myasthenic syndrome (LEMS), were present in 20%-44% of SCD cases[116,122]. A recent study found that the intrathecal injection of P/Q-type VGCC antibodies from PCD led to ataxia in mice, suggesting a pathogenic role in the development of PCD[123]. It is also interesting that LEMS was reported to be present in 16%-40% of SCD cases associated with lung cancer[116,122]. Serum from a patient with SCD without typical onconeural antibodies showed reactivity to protein kinase C of the Purkinje cells[121], which may suggest another immune response-mediated mechanism. In addition, ZIC antibodies were identified in 15% of patients with SCD and SCLC[124], although the role of ZIC antibodies in the development of SCD is not fully understood.

The clinical presentation of SCD includes ataxia, diplopia, nystagmus, dysphagia, dysarthria, vertigo, dizziness, nausea, and vomiting[2,92]. Nystagmus and positional vertigo have also been reported[118,125]. In contrast to LEMS, the treatment of the tumor and/or immunomodulation have not been reported to alter the course of SCD[122]. This finding might be due to a difference in the reversibility of VGCC-induced damage to terminal neurons and Purkinje cells in the cerebellum. However, early treatment after onset has the potential to improve these symptoms[126,127].

LEMS

LEMS is a presynaptic disorder of neuromuscular transmission characterized by impaired quantal release of acetylcholine, which causes proximal muscle weakness, depressed tendon reflexes, and post-tetanic potentiation, as well as autonomic changes[128]. Approximately 50% of patients with LEMS have a tumor[129,130]. The tumor type that occurs in these patients is almost always SCLC, although there have been a few reports of NSCLC[130,131]. Higher frequencies of limited disease in patients with SCLC-LEMS have been reported than in patients with SCLC without LEMS (66% *vs* 40%), most likely because of early detection[132]. In almost all patients (96%), SCLC was found within 1 year of LEMS diagnosis[132]. In the most patients, a symptom of LEMS comes first, and then SCLC is diagnosed. In only 7% of SCLC-LEMS cases, the diagnosis of SCLC preceded the recognition of LEMS[132].

The diagnosis of LEMS is based on clinical symptoms and signs, electrophysiological studies, and the detection of autoantibodies (Table 7)[133]. In 80% of patients, the first symptom is muscle weakness of proximal legs[134]. The muscle weakness usually spreads proximal to distal regions, involving the feet and hands, and caudal to cranial regions, finally reaching the oculobulbar regions[133]. It has been reported that the rapidity of development is more significant in SCLC-LEMS compared with LEMS without SCLC[134]. In contrast to myasthenia gravis (MG), limited muscle weakness of the external eye regions is rarely observed[133]. Characteristically, the impaired reflexes and the muscle weakness can improve after a brief isometric muscle contraction (post-exercise facilitation)[135]. However, a lack of facilitation does not exclude a diagnosis of LEMS[135]. Autonomic dysfunction is also found in more than 80% of patients with LEMS[129,130,134,136]. The most common symptom of autonomic dysfunction is dry mouth, and others include constipation and erectile dysfunction in men[133]. Even if a patient does not volunteer the presence of these symptoms, it is important to specifically inquire about them[135].

On electrodiagnostic study, the first compound muscle action potential (CMAP) amplitude is low in the basal condition, and it becomes even lower at low-frequency stimulation (2-5 Hz)[133]. This phenomenon is due to a lack of release of Ach molecules at the junction. In contrast, post-exercise stimulation or high-frequency stimulation (50 Hz) results in an increase in CMAP amplitude. The easiest and most reliable means of repairing the transmission defect is to provide a brief isometric

voluntary muscle contraction and to measure the CMAP amplitude before and after exercise[135]. In typical patients with LEMS, the amplitude increases significantly, by greater than 100%, which establishes the presynaptic blockage of the neuromuscular transmission[135]. Although comparable sensitivity has been reported at high-frequency stimulation, this test should be avoided if possible because it is very painful[133]. A greater than 100% increase in post-exercise stimulation or high-frequency stimulation has a sensitivity of 78%-85% and a specificity of 100% for LEMS[137,138]. A cut-off of a 60% increase showed a sensitivity of 97% for LEMS and a specificity of 99% for excluding MG[137]. In practice, an increase in the amplitude to greater than 60% in several muscles can be used to confirm the diagnosis[135]. Higher diagnostic sensitivity with the 10-second exercise compared with 30-second exercise has been reported[139].

Antibodies against the P/Q-type VGCC are elevated in more than 95% of patients with SCLC-LEMS, whereas antibodies against the N-type VGCC are elevated in approximately 40% of these patients[135]. These antibodies are also elevated in approximately 70% of patients with LEMS without tumors[135]. Patients who are positive for N-type VGCC antibodies usually have the P/Q-type VGCC. However, two cases with only N-type VGCC antibodies have also been reported in patients with squamous cell lung carcinoma[140]. Although it has been reported that P/Q-type VGCC antibodies are very specific for LEMS, they have also been detected in 1%-4% of patients with SCLC without any neurological dysfunction[133]. SOX1 is the antigen recognized by anti-glial nuclear antibody-positive sera[117]. SOX1 antibodies were present in 64% of patients with LEMS and SCLC but in no patients with idiopathic LEMS[117]. In another report that assessed several types of SOX, SOX antibodies had a sensitivity of 67% and a specificity of 95% for discriminating between LEMS with SCLC and non-tumor LEMS[141].

The treatment of LEMS is threefold, including treatment of the underlying cancer, symptomatic treatment, and immunotherapy[135]. After the detection of cancer, the patient should be treated accordingly. It is important to remember that two-thirds of patients with SCLC-LEMS have a limited form of the disease, in which effective treatment could lead to sustained clinical remission[132,142,143]. The 3,4-diaminopyridine has been used as the first-line treatment for the patients with symptomatic LEMS[133]. This agent blocks VGKC, and prolongs the opening time of VGCC and the action potentials at terminals of the motor nerves[135,144]. As a result, there is an increase in the influx of calcium into the nerve terminal, which is subsequently followed by a release of Ach[135]. A recent study showed that aminopyridines could target the VGCC β subunit leading to enhancement of synaptic and neuromuscular transmission[145]. Four controlled trials of 3,4-diaminopyridine compared with placebo in a total of 54 patients with LEMS reported significant improvements in the primary outcome, muscle strength score, or myometric limb measurement for hours to one week following treatment and significant improvements in the resting CMAP amplitude following 3,4-diaminopyridine administration[128,146-149]. Adverse events reported for 3,4-diaminopyridine treatment during the trials include epigastric discomfort, brief perioral tingling, digital paresthesia, and insomnia[128,146-149]. The starting dose is 5-10 mg 3-4 times per day, and a maximum dose is 60-80 mg per day[135,150]. The risk of seizures increases in a dose-dependent manner although it is mostly reported by administration of approximately 100 mg per day[133,146,148,150]. In addition, treatment with prednisolone and azathioprine for long time might be chosen if some symptoms remain[133]. In 46 of 104 (44%) patients with SCLC-LEMS, prednisolone was required, and in many patients, azathioprine was also administered for the management of LEMS[133]. However, the effects of corticosteroids and immunosuppressive agents have not been tested in randomized controlled trials. A single cross-over trial reported a significant improvement in myometric limb strength with intravenous immunoglobulin (IVIg) compared to placebo[151]. IVIg treatment resulted in an improvement in resting CMAP amplitudes compared with placebo, but this difference did not reach statistical significance[151]. However, a combination of 3,4-diaminopyridine, prednisolone, and azathioprine could lead to the satisfactory management in most patients with SCLC-LEMS, in addition to chemotherapy[133].

CGP

Pseudo-obstruction as a paraneoplastic manifestation of SCLC was first reported in 1975[152]. An autopsy of a patient who had abdominal pain and obstipation revealed autonomic neuropathy limited to the gastrointestinal tract, which was considered to be a remote effect of carcinoma[152]. CGP is now a well-known autonomic neuropathy[153]. This syndrome is characterized by severe gastrointestinal dysmotility without evidence of mechanical obstruction, leading to chronic pseudo-obstruction accompanied by abdominal pain, nausea, vomiting, and, more frequently, severe constipation[92,153]. Gastroparesis is a disorder of the stomach caused by delayed gastric emptying in the absence of mechanical obstruction[154]. Gastroparesis has been described as a complication of several malignancies, including lung cancers, although diabetes mellitus is the most common identifiable cause of benign gastroparesis[154]. This "malignant gastroparesis" includes postvagotomy syndrome, cancer invasion to the autonomic nervous system, and paraneoplastic dysmotility of the stomach as a subtype of CGP[154].

In an analysis of 162 anti-Hu antibody-positive patients, 142 patients (88%) had cancer[155]. Of these 142 patients, SCLC was proven in 132 (93%). Although sensory neuropathy was the most common neurologic syndrome, 23% of patients had gastrointestinal symptoms[155]. In another report, anti-Hu antibody was detected in 8 of 9 patients with CGP associated with SCLC (one patient was not tested)[156]. CGP is often the first

manifestation of the malignancy[155,157]. Although SCLC is most common in CGP, NSCLC has also been described as an underlying malignancy[155,156].

Histopathology has shown marked mononuclear cell infiltration of the myenteric plexus with less involvement of the submucosal plexus and a decrease in the number of myenteric plexus neurons[158]. Immunohistochemical staining showed infiltration by a mixture of B-cell and T-cell lymphocytes and plasma cells, and sparse and disorganized interstitial cells of the Cajal network[158,159]. The inflammatory/immune response in enteric ganglionitis leads to neuronal dysfunction and degeneration over time and sometimes results in the complete loss of enteric neurons[160]. The early treatment of cancer appears to offer the greatest chance for the improvement of CGP[161]. A case of successful treatment with octreotide, a somatostatin analog, has also been reported[153].

Polymyositis /dermatomyositis

Polymyositis (PM)/dermatomyositis (DM) is an autoimmune-based systemic inflammatory myopathy. In the case of DM, the characteristic cutaneous manifestations include scaly and erythematous plaques on the dorsal sides of the both hands (Gottron's sign), edematous rash of the eyelids and periorbita (heliotrope rash), photosensitive poikilodermatous eruptions, and periungual telangiectasia[92]. In a review of 2439 patients with DM, 574 patients (24%) have been reported to be associated with malignancy, and 97 (10.2%) of 947 patients with PM had an associated malignancy[162]. A wide variety of malignancies has been associated with DM and are significantly influenced by the patient ethnicity[162]. Carcinomas of the nasopharynx (21%), breast (15%), lung (15%), ovary (9%), and colon (5%) have been reported as the most common malignancies associated with DM[162-166]. In an analysis of population-based cohorts derived from the Caucasian populations of Sweden, Denmark, and Finland, 115 of 618 patients (18.6%) with DM developed malignancies after the diagnosis of DM[167]. The types of malignancy that increase in relative risk significantly were carcinomas of ovary (standardized incidence ratio 10.5), lung (5.9), pancreas (3.8), stomach (3.5), and non-Hodgkin's lymphoma (3.6)[167]. In a report of 138 Chinese patients with DM and cancer, the most common malignancies were carcinomas of nasopharynx, breast, and the lung[168]. More severe signs and symptoms in skin and muscle often indicates an underlying malignancy in patients with DM[162]. The characteristic cutaneous manifestations associated with malignancy include cutaneous leukocytoclastic vasculitis[169], bullous DM[170], cutaneous necrosis[164,165], periungual erythema[165], and necrotizing myopathy[171]. Regarding myositis-specific antibodies, a low frequency of anti-Jo-1 antibody has been reported in cancer-associated myositis, whereas anti-p155/140 antibodies have been identified in 50% of cancer-associated myositis cases, much higher than in non-cancer-associated myositis (4.1%)[172].

In PM/DM associated with lung cancer, the common histological types were SCLC (29%) and squamous cell carcinoma (21%)[173]. PM/DM associated with lung adenocarcinoma appears to be rare[171,174,175]. A case of PM with bronchopulmonary carcinoid has also been reported[176]. The onset of PM/DM is frequently observed before the diagnosis of lung cancer[173].

The role of internal malignancies in the development of DM remains controversial. Several case reports have highlighted a causal role of cancer on development of DM because DM significantly improved after the successful therapy of lung cancer[162,174,177]. Furthermore, among 22 patients with cancer-associated DM who received effective antitumor therapy, 16 patients (73%) experienced remission of DM[178]. In contrast, the improvement of DM after treatment for cancer has been observed only in 18%-37% of cases[179-183]. It has been reported that myositis-associated autoantigens, Jo-1 and Mi-2, were expressed at high levels in myositis muscle, particularly in regenerating muscle fibers, and in adenocarcinomas of the lung and breast, but not in the corresponding healthy tissues[162,184]. Thus, a model of "cross-over" immunity was proposed in which an initial cellular immune response directed at tumor cells overexpressing antigens can also target muscles commonly expressing antigens in patients with myositis[162,184]. In this setting, a causative role of malignancy in the development of DM can be considered. However, malignancy may also trigger the development of DM. In a case report, DM developed in a patient with SCLC, and the DM went into remission after the successful treatment of SCLC. The DM recurred 10 years later without any malignancy[180]. In this case, internal malignancy was not a prerequisite for DM relapse; the patient had had an occult autoimmune mechanism of DM. SCLC triggered the expansion of an autoreactive T cell clone as an autoantigen, and DM resulted[180]. Because of the aging of the immune system, the autoreactive clone gradually increased over 10 years and induced DM again[180].

A combination of corticosteroids and tumor resection or chemotherapy can improve the symptoms of DM associated with lung cancer[173,180]. It has also been reported that an epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), gefitinib, resulted in the dramatic recovery of a patient with DM associated with adenocarcinoma[174].

Opsoclonus-myoclonus

Opsoclonus-myoclonus (OM), or opsoclonus-myoclonus-ataxia (OMA), is a unique movement disorder characterized by conjugate, randomly directed, rapid eye movements (opsoclonus) and by myoclonus occurring in the face, head/neck, trunk, and limbs[185]. Some patients also exhibit cerebellar dysfunction with dysarthria and truncal ataxia, and a few become confused or even comatose[186]. Various etiologies have been implicated in OM, including infectious, toxic, metabolic, degenerative, and paraneoplastic disorders[185]. An underlying malignancy accounts for 20% of cases with OM[187]. In

a Spanish survey in which infectious, toxic, or metabolic disorders were excluded, 14 (58%) of 24 patients with OM were paraneoplastic, and the remaining 10 cases were idiopathic[186]. Among tumors associated with OM, the most common were SCLC (9 patients; 64%) and breast cancer (2 patients; 14%). Rarely, NSCLC has also been reported[186,188-191]. Antineural antibodies have been found in only a few patients with paraneoplastic OM[186]. Antineural antibodies detected in lung cancer include anti-Ri[190,192], anti-Hu[186,191], anti-amphiphysin[186], and P/Q-type VGCC[191] antibodies. A case of OM associated with SCLC with a high anti-mitochondrial antibody titer has also been reported[193].

In contrast to most of the other PNSs, paraneoplastic OM may remit either spontaneously, following the treatment of the tumor, or in association with clonazepam or thiamine treatment[194]. Paraneoplastic OM has been reported to exhibit a more severe clinical course than idiopathic OM, despite treatment with IVIg or corticosteroids[186]. When underlying tumors were treated, however, a complete or partial neurological recovery could be observed[186]. With appropriate treatment for SCLC, approximately half of reported patients have experienced improvements in neurologic function[195]. Tumor control is essential for the successful long-term management of paraneoplastic OM.

Subacute sensory neuropathy

A diagnosis of subacute sensory neuropathy (SSN) could be performed when the following criteria are all fulfilled: subacute development in less than 12 wk, severity of at least 3 (moderate disability) assessed by a Rankin score, onset of numbness with often pain and sensory disturbance, involvement of arms and legs (so-called gloves and stockings area), and often asymmetry at onset. Furthermore, electrophysiological findings have shown the significant sensory fibers disturbance and, in at least one sensory nerve, the absence of sensory nerve action potentials sensory nerve[93]. The motor nerves may also be minimally disturbed[196]. Tendon reflexes are depressed or absent[194], and patients often exhibit autonomic, cerebellar, or cerebral abnormalities[196]. SSN occurs in approximately 75% of patients with paraneoplastic encephalomyelitis, is predominant in 50%, and is clinically pure in 25%[194,197,198]. In a review of 26 patients with paraneoplastic SSN, 19 (73%) had SCLC[196]. There was a striking predominance of females (20:6)[196]. SSN usually predates the diagnosis of cancer, with a median delay of 3.5-4.5 mo[194,197,198].

SSN in patients with SCLC is typically associated with anti-Hu antibody[194,199]. Less frequently, SSN in patients with SCLC is associated with anti-CV2 (CRMP-5), anti-amphiphysin, or anti-Yo antibodies[194,199]. A patient with SSN associated with SCLC who was positive for ganglionic neuronal acetylcholine receptor (nAChR) antibody has been reported[200].

The early treatment of the underlying tumor appears to offer the best chance of stabilizing the neurological symptoms[198]. The complete response of SCLC appears to produce an improvement in neurological function[100,106,201]. Several cases of spontaneous SCLC regression and SSN progression have been reported, suggesting a host immune response directed at both the cancer and the nervous system[100-102]. However, immunotherapy consisting of corticosteroids, plasma exchange, and IVIg is ineffective in most cases[194,201,202].

PARANEOPLASTIC DERMATOLOGIC SYNDROMES

The paraneoplastic dermatologic syndromes associated with lung cancer are presented in Table 8. Several dermatologic syndromes represent very specific conditions that suggest the presence of associated lung cancer. In the paraneoplastic cases, the responsiveness to the therapy is generally weaker compared with the non-paraneoplastic equivalents[2]. Dermatomyositis is involved in neurologic, dermatologic, and rheumatologic syndromes. We describe dermatomyositis as a PNS because both the neuromuscular system and the skin are affected. Generally, paraneoplastic dermatologic syndromes improve in response to the treatment of the underlying neoplasm; the efficacy of ectopic local treatments is partial or insufficient.

Acrokeratosis paraneoplastica (Bazex syndrome)

The typical features of acrokeratosis paraneoplastica, also called Bazex syndrome, are erythematous scaly lesions on the extremities, ears, and bridge of the nose in association with a malignancy[203]. The most common malignancies are squamous cell carcinomas of the laryngopharyngeal region or of the esophagus, tongue, or lung[203,204]. Other histological types of lung cancer, such as adenocarcinoma and SCLC, have also been reported, although squamous cell carcinoma is the most common[204-207]. In a review of 109 patients, psoriasiform lesions preceded the diagnosis of the associated malignancy in 73 (67%) patients, whereas cutaneous manifestations followed the diagnosis of the neoplasm in only 16 (15%) of 109 patients[204]. The cutaneous lesions are erythematous to violaceous in color with an associated scaling eruption, and the most common sites of involvement are the ears, nose, hands, and feet, including the nails[204,208]. These lesions are typically non-pruritic, have ill-defined margins, and are symmetric[209,210]. The psoriasiform dermatitis begins in the fingers, toes, nose, and helix of the ears and progresses to involve the palms, soles, and cheeks, finally extending centripetally to the arms, legs, scalp, and trunk[205,211].

The underlying mechanisms of acrokeratosis paraneoplastica have not been elucidated. One theory proposes that antibodies against the tumor cross-react with keratinocyte or basement membrane antigens[210]. Alternatively, a T cell-mediated immune response to tumor-like antigens in the epidermis has been proposed[210]. Squamous cell carcinoma lines have been shown to synthesize and secrete growth factors, such as transforming growth fac-

Table 8 Paraneoplastic dermatologic syndromes and paraneoplastic rheumatologic syndromes associated with lung cancer

Paraneoplastic dermatologic syndromes associated with lung cancer
Polymyositis/dermatomyositis
Acrokeratosis paraneoplastica (Bazex syndrome)
Acanthosis nigricans
Tripe palms
The sign of Leser-Trélat
Erythema gyratum repens
Cutaneous leukocytoclastic vasculitis
Pityriasis rubra pilaris
Rhinophyma
Eosinophilic cellulitis
Herperiformis pemphigus
Hypertrichosis lanuginose acquisita
Erythema elevatum diutinum
Paraneoplastic rheumatologic syndromes associated with lung cancer
Polymyositis/dermatomyositis
Vasculitis
Cutaneous leukocytoclastic vasculitis
Henoch-Schönlein purpura
Hypertrophic pulmonary osteoarthropathy
Remitting seronegative symmetrical synovitis with pitting edema
Polymyalgia rheumatica

tor (TGF)-1, which is active in autocrine growth[212,213]. The excessive expression of growth factors by the tumor might lead to epidermal hyperplasia and cancer cell proliferation.

The treatment of the underlying neoplasm often significantly improves the cutaneous symptoms[210]. For some patients, cutaneous lesions, most commonly nail dystrophy, may persist despite successful tumor eradication[210].

Acanthosis nigricans, tripe palms and the sign of Leser-Trélat

The characteristic manifestations of acanthosis nigricans (AN) are thickening and hyperpigmention of the skin, and develop predominantly in the neck to axilla[2]. Although AN is usually observed in benign conditions accompanied by endocrinopathies, such as insulin resistance, obesity, erythema nodosum, or medications such as sex hormones or nicotinic acid[2,214], a paraneoplastic form has also been documented. Among paraneoplastic AN cases, the most common histologic type is adenocarcinoma, of which 70%-90% are located intra-abdominally and 55%-61% are gastric adenocarcinomas[215]. Less commonly, paraneoplastic AN is associated with NSCLC[216-218]. The major features of AN are darkening and thickening of the skin (hyperkeratosis), which occurs mainly in the folds of the skin in the axilla, groin, and back of the neck[216]. Oral lesions, observed in 50% of cases, are generally located on the lips, tongue, and buccal mucosa[219]. Gross and eruptive AN with florid cutaneous papillomatosis and palmar/plantar keratoderma are typical features of AN associated with malignancy[215]. Rapid onset is also typical in paraneoplastic dermatoses[219].

"Tripe palms" is also known as acanthosis palmaris, pachydermatoglyphy (PDG) or palmar hyperkeratosis[220]. This condition is characterized by a yellowish rugose hypertrophy of the palms and sometimes the soles, leading to an exaggeration of the skin lines[218,221]. Tripe palms are usually associated with AN. More than 90% of cases are associated with neoplasms; in the majority of these cases, lung and gastric cancers are the underlying malignancies[218,221].

The sign of Leser-Trélat (LT) refers to the eruption of numerous seborrheic keratoses[215]. A rapid onset, rather than the number of seborrheic keratoses, suggests the presence of an underlying malignancy[219]. Although gastric adenocarcinoma is the most common malignancy[215,219], NSCLC has also been reported[217,222]. In patients with tripe palms, the coexistence of AN (72%) and LT (10%) has been reported[219,221].

The pathogenesis of AN is poorly understood. However, one possibility is that interactions between excessive amounts of circulating insulin with insulin-like growth factor receptors on keratinocytes and dermal fibroblasts lead to the development of AN[223]. An increased production of TGF-α by the tumor could be responsible for an increased proliferation of keratinocytes and the development of paraneoplastic AN[217,218]. No specific treatment has been established for AN. However, the treatment of the underlying malignancy usually improves AN as well[215].

Erythema gyratum repens

Erythema gyratum repens (EGR) is rare, and the primary lesion is a serpiginous macular, occasionally popular, erythema[210]. Most of the body is covered in numerous serpiginous bands arranged in a parallel configuration of concentric red swirls or a wood-grain pattern resembling a knotty cypress board[210,224]. *Gyratum* means "coiled or winding around a central point", and *repens*, from the Latin, means "to crawl or creep"; the name itself describes the classic eruption of concentric erythematous rings, which develop a trailing scale at their edges and advance at a rapid rate ($\leqslant$ 1 cm per day)[224]. All reported patients with EGR have been Caucasian[210]. In a review of 49 cases of EGR, 41 (84%) were associated with a neoplasm, most commonly of the lung[225]. Cases of NSCLC, including adenocarcinoma and squamous cell carcinoma, but not SCLC, have been reported[224,226-228]. The skin symptoms usually disappear with therapy for the underlying lung cancer[225,227,228].

Cutaneous leukocytoclastic vasculitis

Cutaneous leukocytoclastic vasculitis (CLV) is an inflammatory vascular disease characterized by the prominent involvement of the skin and the infiltration of the small blood vessels with polymorphonuclear leukocytes and the presence of leukocytosis, fibrinoid necrosis, and extravasation of red blood cells[229]. In cases of paraneoplastic vasculitis, CLV (45%) and polyarteritis nodosa (36.7%) were the most frequently observed subtypes of vasculitis[230]. In 71% of CLV cases, manifestations of vasculitis

appeared before or concurrent with the initial identification of the tumor or at the relapse of the tumor[231]. The most common malignancies were hematologic malignancies and carcinomas of urinary organs, gastrointestinal tract, and lung (20%-26%)[231,232]. The associated lung cancers were adenocarcinoma and squamous cell carcinomas[229,231-233]. The mechanism by which neoplasms cause vasculitis has not been defined. However, it has been postulated that tumor antigens may induce immune complexes, which could be deposited on blood vessel walls, stimulating a direct autoimmune reaction against the host' s vessels; alternatively, the tumor emboli or the tumors themselves may invade the vascular structures[231,233].

The rash associated with CLV can present as a multitude of morphologic appearances, including urticaria, purpura, hemorrhagic vesicles, ulcers, nodules, livedo reticulares, infarcts, or digital gangrene; a skin biopsy is the gold standard for the diagnosis of CLV[233,234]. The rash is usually symmetric and most commonly involves the lower extremities, often accompanied by pain or burning[2,233]. Most patients demonstrate concordance of disease activity and treatment response for both cancer and vasculitis[232]. Treatments for vasculitis include corticosteroids and immunosuppressants, such as cyclophosphamide[230]. Successful surgical resection of lung cancer has resulted in the complete improvement of the skin rash in a few cases[229,233].

PARANEOPLASTIC RHEUMATOLOGIC SYNDROMES

Many rheumatologic syndromes, such as rheumatic arthritis and systemic lupus erythematosus occur without an association with malignancy[2]. However, several conditions have been reported to be associated with lung cancer (Table 8). Dermatomyositis is a symptom of several conditions, such as neurologic, dermatologic, and rheumatologic syndromes. In addition to the standard treatments for the non-paraneoplastic cases, the therapy directed to the cancer is important for the management of paraneoplastic rheumatologic syndromes[2]. The paraneoplastic cases are generally less responsive to therapy compared with their non-paraneoplastic cases[2]. We describe hypertrophic pulmonary osteoarthropathy (TPO) as a rheumatic syndrome here, although it may also be classified as a skeletal syndrome[1].

Hypertrophic pulmonary osteoarthropathy

Hypertrophic osteoarthropathy (HOA) is characterized by the abnormal proliferation of the cutaneous and osseous tissues at the distal regions of the extremities[235,236]. The triad of clinical signs and symptoms includes clubbed fingers, symmetric polyarthritis, and periostitis of the long tubular bones[237,238]. Hypertrophic pulmonary osteoarthropathy (HPO) is defined as HOA secondary to pulmonary disease[239]; it is frequently described in association with lung cancer, cystic fibrosis, or right-to-left cardiac shunts[235]. More than 70% of HPO cases are associated with lung cancer[237,239]. In a review of 2625 lung cancer cases, 19 patients (0.72%) were found to have HPO[239]. Of 19 lung cancers, 10 (53%) were adenocarcinomas and 4 (21%) were squamous cell carcinomas[239]. HPO differs from rheumatoid arthritis in several key ways: the presence of non-inflammatory synovial fluid, a lack of radiographic erosions of the joints, negative rheumatoid factor, and pain that involves both joints and bones[238]. Periostitis is the hallmark of HPO. Most cases involve the tibiae and fibulae, and severe cases have included all the tubular bones, such as ulnae and femurs[238]. Bone radiography reveals periosteal membrane thickening and periosteal new bone formation[237,239]. Unlike osteoarthritis, HPO is not associated with joint space narrowing or subchondral sclerosis[238]. Bone scintigraphy is a useful, widespread medical imaging procedure that facilitates the detection of HPO[239]. Characteristic findings include symmetric bilateral increased uptake in the long bones[238]. Although FDG-PET may also show diffusely increased FDG uptake in the periosteal lesions[240,241], the reliability of FDG-PET in the diagnosis of HPO has not been established.

Although the exact mechanism of HOA remains unclear, several theories have been proposed[237,238,242]. The most promising explanation involves megakaryocytes and platelet clumps. Megakaryocytes continually emerge from the bone marrow; they are trapped by the pulmonary capillary bed and fragment there into platelets[242]. In disorders in which megakaryocytes or megakaryocyte fragments bypass the pulmonary capillary network, these large particles can enter the systemic circulation and reach the fingertips in axial vascular streams[237,242]. These large megakaryocyte fragments then interact with endothelial cells, leading to the release of growth factors, including platelet-derived growth factor (PDGF), prostaglandin E, and vascular endothelial growth factor (VEGF)[238]. These growth factors cause fibroblast proliferation, digital clubbing, vascular hyperplasia, edema, and new bone formation[237,238,243]. Significantly higher levels of PDGF and VEGF have been reported in HOA patients compared with healthy controls or subjects with pulmonary diseases other than HOA[244-246].

Conventional analgesic medications, including nonsteroidal anti-inflammatory drugs, have limited effects on HPO. In contrast, the treatment of lung cancer often resolves HPO[237,238,247-249]. In particular, the complete resection of lung cancer may result in long-term improvements in HPO[248,249]. The successful treatment of HPO with gefitinib has also been reported in a case of lung adenocarcinoma[250]. Recently, it was reported that bisphosphonates (pamidronate or zoledronic acid) could dramatically resolve pain and swelling related to HPO[235,251,252]. Although the mechanism of bisphosphonate-mediated improvement of HPO is unclear, the anti-tumor and anti-inflammatory effects of these drugs might be beneficial. In this regard, it has been reported that pamidronate is a potent inhibitor of VEGF[253]. In addition, the effectiveness of octreotide in relieving pain in patients with HPO

has been reported[254,255]. Subcutaneous octreotide at a dose of 100 g twice daily resulted in complete pain relief within several days[254,255]. Octreotide has been reported to indirectly exert anti-angiogenic activity by inhibiting growth factors, including VEGF, or *via* immunomodulatory effects[256]. Based on a role of VEGF in the pathogenesis of HPO, an anti-VEGF antibody, bevacizumab, might also be a potent therapeutic option.

PARANEOPLASTIC HEMATOLOGIC SYNDROMES

Paraneoplastic hematologic syndromes are often asymptomatic and are usually detected after the diagnosis of cancer, typically in the advanced stage of the disease[2]. There is no specific treatment for these conditions, and the successful therapy for lung cancer may often improve hematologic disorders as well. In general, patients with hematologic syndromes have been reported to have a poor prognosis.

Granulocytosis (neutrophilia)

An increased level of white blood cells (leukocytosis) is often found in patients with lung cancer, either at the time of diagnosis or during the course of the disease[257]. Leukocytosis may be caused by one or more factors, such as concomitant infections or the administration of corticosteroids[257]. When leukocytosis is observed in the absence of these conditions, tumor-related leukocytosis should be considered. Occasionally, extreme leukocytosis ($> 50000/mm^3$ or even more than $140000/mm^3$) has been reported[258]. In an analysis of 227 patients with lung cancer, 33 patients (14.5%) were diagnosed with tumor-related leukocytosis ($> 10000/mm^3$)[257]. The associated histology in 14 (42%) patients was adenocarcinomas, 12 (36%) squamous cell carcinomas, 6 (18%) large cell carcinomas, and only 1 (3%) SCLC. However, the highest frequency of association was observed in large cell carcinomas (54.5%; 6 of 11 patients). The majority of the patients had granulocytosis. Of 33 patients, 16 exhibited high serum G-CSF levels (47-1103 pg/mL), 4 patients had high serum GM-CSF levels (31-61 pg/mL), and 18 patients had high serum IL-6 levels (11-1060 pg/mL)[257]. In addition, 12 specimens exhibited positive staining against anti-G-CSF antibody, suggesting a G-CSF-producing lung cancer. Bone marrow examinations revealed a massively increased and left-shifted granulopoiesis extending to the myeloblasts, as typically develops under G-CSF stimulation[258]. In contrast to leukemic blasts, the mature neutrophils that characterize paraneoplastic leukocytosis do not cause hyperviscosity or vaso-occlusion, and therefore do not require specific therapy[2]. Patients with tumor-related leukocytosis have been reported to have a poor prognosis[9,257,259]. The survival of patients with hypercalcemia and leukocytosis (MST 1.5 mo) was significantly shorter than that of patients with hypercalcemia alone (MST 3.8 mo)[9]. Hypercalcemia and leukocytosis can occur through a common mechanism, *i.e.*, long-term exposure to G-CSF[9]. "Hypercalcemia-leukocytosis syndrome" has been proposed as a clinical entity of paraneoplastic syndrome, and it may indicate a poorer outcome in lung cancer[9].

Hypereosinophilia

Excessive eosinophilia (hypereosinophilia) is a phenomenon associated with a wide variety of allergic diseases, parasitic infections, certain forms of vasculitis, and medications. Excessive eosinophilia has also been associated with malignancies, especially hematologic malignancies, including malignant lymphomas. Although case reports have described patients with various solid tumors and excessive eosinophilia, this association is thought to be less common[260]. Several reports have described excessive eosinophilia associated with lung cancer[260-262]. Hypereosinophilia has been reported in all types of lung cancer, including large cell carcinoma, squamous cell carcinoma, adenocarcinoma, and SCLC[260,261,263,264]. Although the exact pathogenesis of hypereosinophilia associated with lung cancer has not been fully elucidated, bone marrow stimulation *via* circulatory factors secreted by cancer cells is the most widely accepted theory[260,261,265-267]. Interleukin-5 (IL-5) and GM-CSF are the most frequently implicated factors[260,262,265-267]. IL-5 has emerged as a key cytokine that controls the production, activation, and recruitment of eosinophils[260]. In a case report of large cell carcinoma with excessive eosinophilia, the serum IL-5 level was elevated, and immunohistochemical staining of the resected primary tumor revealed large amounts of intracellular IL-5[260]. Both the eosinophil count and IL-5 levels normalized after the surgical removal of the tumor, suggesting that the eosinophilia was mediated by IL-5 produced by the cancer[260]. IL-5 mediates the antitumor cytotoxicity of eosinophils induced by IL-2 against various human tumor cell lines[268]. Nevertheless, hypereosinophilia is generally associated with tumor aggressiveness and poor prognosis[261,265,267]. A poor prognosis may reflect extensive disease and dissemination[260]. The exact functional roles of eosinophils in human cancers remain unclear[260].

Thrombocytosis

Thrombocytosis is generally diagnosed when a platelet count is more than $400000/mm^3$ and is associated with various diseases, including chronic inflammatory diseases and infectious diseases. Thrombocytosis is also frequently observed in patients with various malignancies, including lung cancer[2,269]. The reported prevalence of thrombocytosis at the time of lung cancer diagnosis is 13%-32%[269-271]. Paraneoplastic thrombocytosis is thought to be caused by the production of cytokines from the tumor, and the most representative is IL-6[2,272]. In an analysis of 100 patients with renal cell carcinoma, serum levels of IL-6 were positively correlated with platelet counts[272]. In addition, anti-IL-6 antibody administration reduced platelet counts in all 12 patients tested[272]. This finding suggests that the overproduction of IL-6 is responsible

Table 9 Criteria for the diagnosis of paraneoplastic glomerulopathy

No obvious alternative etiology other than malignancy
Existence of a time relationship between the diagnosis of glomerulopathy and malignancy
Clinical improvement after the complete surgical removal of the tumor or complete remission achieved by chemotherapy/radiotherapy
Deterioration of glomerulopathy associated with recurrence of the malignancy

for paraneoplastic thrombocytosis. Survival in patients with thrombocytosis has been reported to be significantly shorter than in those without thrombocytosis[269-271]. A multivariate analysis of prognostic factors using the Cox proportional hazards model indicated that thrombocytosis was an independent prognostic factor[269,271]. Although the reasons for poor survival in patients with thrombocytosis remain unclear, PDGF may play a role in cancer progression[273,274].

PARANEOPLASTIC GLOMERULOPATHY

Paraneoplastic glomerulopathies are rare manifestations of neoplastic disease, which should be distinguished from iatrogenic renal damage. Criteria for the diagnosis of paraneoplastic glomerulonephropathy have been established (Table 9)[275]. Optimally, a diagnosis of paraneoplastic glomerulopathy should include the establishment of a pathophysiologic link between the tumor and glomerulopathy, including the detection of tumor antigens and antitumor antibodies within subepithelial immune deposits[276]. However, establishing such a connection would be always unnecessary for a clinical diagnosis. In an analysis of 600 patients with lung cancer, the prevalence of proteinuria and hematuria was 10% and 7%, respectively[277]. This relatively high prevalence may be attributed to the study's low cut-off value for proteinuria (0.1 g/d) or the use of the qualitative dipstick test alone to detect hematuria, without an assessment of urinary sediment. However, a prospective case-control study reported a significantly higher prevalence of proteinuria and hematuria in patients with lung cancer compared with asthmatic patients[277]. Regarding the histology of the glomerular diseases, solid tumors, including lung cancer, are preferentially associated with membranous glomerulonephropathy[275,278,279]. Other types of glomerular disease associated with lung cancer have also been reported, including minimal change disease[280], IgA nephropathy[281], focal segmental glomerulosclerosis[282,283], membranoproliferative glomerulonephritis[284], and crescentic glomerulonephritis[285]. These studies reported a variable histology of lung cancer associated with glomerulopathy, including SCLC and NSCLC.

Two thirds of MGN cases are idiopathic[275]. The etiology of secondary MGN frequently includes infections, autoimmune diseases, and drug toxicity[275,286]. In a cohort study of 240 patients with MGN, 24 patients (10%) had a malignancy at the time of renal biopsy or within one year thereafter[286]. Among the patients with cancer and MGN, 40%-45% clinically manifested the nephrotic syndrome prior to the diagnosis of the tumor[276]. Simultaneous presentation occurred in approximately 40% of patients, and in the remaining 15%-20%, glomerular disease became apparent following the diagnosis of the tumor[276]. Regarding the pathogenesis of paraneoplastic MGN, several reports have demonstrated the presence of tumor antigens, such as carcinoembryonic antigen (CEA), in the glomeruli of patients with paraneoplastic MGN[287-289]. The eluate of the glomeruli was found to react specifically with the surface of the cancer cells from the same patient, and it reacted not only with the cancer cell extract but also with CEA[289]. An IgG antibody eluted from the kidney reacted with gastric and colonic carcinomas, and the reactivity was blocked by preincubating the tumor substrate with CEA[289]. These cross-reactions between eluates from glomeruli and tumor antigens provide evidence for a role of the immune complex in the pathogenesis of paraneoplastic glomerulopathy[275,287,289].

PARANEOPLASTIC OPHTHALMOLOGICAL SYNDROMES

Cancer-associated retinopathy

Cancer-associated retinopathy (CAR) is a rare paraneoplastic syndrome that is often associated with SCLC[290]. More than 100 CAR cases have been reported since CAR was first reported in 1976[291], although the precise frequency of CAR in SCLC patients remains unclear. CAR causes progressive visual loss within several months, and it is associated with a triad of symptoms: photosensitivity, ring scotomatous visual field loss, and attenuated retinal arteriole caliber[292]. Retinopathy may occur either before or after the diagnosis of cancer[290]. It is believed that CAR is autoimmune-mediated *via* autoantibodies against retinal photoreceptor proteins, such as recoverin, heat-shock cognate protein 70, enolase, and transient receptor potential cation channel, subfamily M, member 1 (TRPM1)[293-296]. In certain patients with lung cancer, high-titer serum autoantibodies against recoverin trigger the development of CAR[297,298], whereas low-titer serum antibodies of patients with lung cancer do not necessarily cause CAR[299,300]. In addition, the frequencies of serum autoantibodies against recoverin in patients with SCLC or NSCLC without CAR were found to be 15% and 20%, respectively[293]. These values are much higher than the frequency of the development of CAR, suggesting that serum autoantibodies against recoverin do not necessarily trigger the development of CAR. Aberrant expression of recoverin protein resulting from altered demethylation of the recoverin gene can also trigger the host immune response, followed by the development of CAR[301]. Regarding treatment, corticosteroids, in addition to anticancer therapy, may be effective for the control of CAR. In a review of 15 SCLC patients with CAR who received corticosteroids, 13 patients (87.7%) recovered

visual function[290]. In those 13 patients, the mean dose of corticosteroids administered at initial treatment was 57.1 mg (25-100 mg) of prednisolone with or without induction with high-dose methylprednisolone[290]. Lower doses of corticosteroids might not be sufficient to improve visual function[290,302]. In addition, treatment delay after visual symptom onset may lead to irreversible injury to the photoreceptor cells[290,291,302]. An effect of the expressed recoverin on sensitivity to anti-cancer drugs has also been reported[303]. Compared with recoverin-negative control cells, recoverin-transfected lung cancer cells were more sensitive to several anticancer drugs[Matsuo S, 2010]. Aberrantly expressed recoverin may regulate tumor cell proliferation and drug sensitivity to anticancer drugs in patients with CAR[303].

Diffuse uveal melanocytic proliferation

Diffuse uveal melanocytic proliferation (DUMP) is a rare paraneoplastic syndrome characterized by: (1) multiple round or oval, subtle, red patches at the level of the retinal pigment epithelium in the posterior fundus; (2) a striking pattern of multifocal areas of early hyperfluorescence corresponding to these patches; (3) the development of multiple, slightly elevated, pigmented and non-pigmented uveal melanocytic tumors, as well as evidence of diffuse thickening of the uveal tract; (4) exudative retinal detachments; and (5) rapidly progressive cataracts[304,305]. More than 30 cases of DUMP have been reported; almost all of the cases were bilateral, except for one report of unilateral DUMP associated with SCLC[306]. The most common associated malignancies are ovarian carcinoma in women and lung and pancreatic cancers in men[307]. On histology, NSCLC (adenocarcinoma, large cell carcinoma, and squamous cell carcinoma) and SCLC have been reported[306-309]. In half of the cases, DUMP manifests before the diagnosis of an underlying malignancy[310]. Cutaneous and/or mucosal focal melanocytic proliferation has also been observed in several cases[310]. It is believed that protein release from the primary cancer may incite an antibody response, which may cross-react with the ocular tissue[309]. Another pathogenic mechanism may include hormonal stimuli from the cancer, leading to ocular melanocytic proliferation[309]. The treatment of DUMP with systemic corticosteroids and orbital radiotherapy is ineffective[308]. However, the regression of DUMP can be achieved by resecting the underlying lung cancer[308].

PARANEOPLASTIC COAGULOPATHY

Trousseau's syndrome

In 1865, Armand Trousseau reported that unexpected and migratory thrombophlebitis could be the first symptom of visceral cancer[311]. Ironically, two years later, he found the thrombophlebitis on himself, and was died of development of gastric cancer. Similar descriptions were repeated and extended over the years. Sack *et al*[312] reviewed 182 patients with chronic disseminated intravascular coagulopathy (DIC) and malignancy, in whom migratory thrombophlebitis, arterial emboli in various organs, and hemorrhage were frequently observed. Hematologic data showed abnormalities associated with intravascular coagulation, such as hypofibrinogenemia and thrombocytopenia. Other abnormalities included prolonged prothrombin time, increased fibrinogen-fibrin degradation products, microangiopathic hemolytic anemia, and verrucous endocarditis[312]. More recently, the term "Trousseau's syndrome" is sometimes even applied to patients who already have an advanced malignancy and then develop some form of thrombosis[313]. Multiple definitions of Trousseau's syndrome have been proposed, ranging from the classic "occurrence of migratory thrombophlebitis with visceral cancer" to simply "carcinoma-induced coagulopathy", "hypercoagulability syndrome associated with cancer", and "malignancy-related thromboembolism"[313]. Multiple mechanisms of Trousseau's syndrome have also been described[313]. Intravascular coagulation (thrombosis or DIC) has been most frequently associated with mucin-producing adenocarcinomas[314]. Mucins can initiate intravascular coagulation by activating factor X[314]. Injecting carcinoma mucins into mice generated platelet-rich microthrombi dependent on P- and L-selectin, but not thrombin[315]. The release of tissue factor (TF) and cysteine protease from cancer *via* the activation of factor X has also been reported in the pathogenesis of Trousseau's syndrome[313]. Hypoxia may increase the expression of genes that facilitate coagulation, including TF and plasminogen activator inhibitor-1 (PAI-1)[316].

The incidence of thrombosis in 537 patients with lung cancer was assessed[317]. A total of 39 venous thrombotic events (VTEs), including 17 deep venous thrombi, 15 pulmonary emboli, and 7 cases of both deep venous thrombi and pulmonary emboli, were observed over 879 person-years of follow-up, resulting in 44.4 venous thrombic events per 1000 person-years[317]. After adjusting for age and sex, the estimated thrombotic risk in lung cancer patients was 20-fold higher than in the general population[317]. Patients with adenocarcinoma had a higher risk than patients with squamous cell carcinoma (66.7 and 21.2 per 1000 person-years, respectively)[317]. Patients with distant metastasis had a 6-fold increased risk compared with patients with localized tumors[317]. It should be noted that the risk of venous thrombosis increases 3-fold when chemotherapy is started compared with the time when no chemotherapy has been administered[317].

Heparin has been widely used as the preferred treatment for Trousseau's syndrome[312,318]. A therapeutic range of 1.5-2.5 times the baseline activated partial thromboplastin time (APTT) has been recommended[319]. Heparin binds to antithrombin Ⅲ, causing its activation and leading to the inactivation of thrombin and other proteases, such as factor Xa. Heparin prevents the binding of mucin to L- and P-selectins and mucin-induced microthrombi[315]. Trousseau's syndrome is often resistant to warfarin, which inhibits fluid-phase coagulation but not selectins[315]. A serious side effect of heparin is hep-

arin-induced thrombocytopenia (HIT), which involves an immunological reaction that causes platelets to be targeted by the immunological response and results in the degradation of platelets, resulting in thrombocytopenia. Recently, low-molecular-weight heparins (LMWHs) have become popular treatments for Trousseau's syndrome, in part because of their greater bioavailability, the ability to administer single daily doses, the reduced incidence of HIT, and possibly improved safety[320,321]. Successful treatment with long-term LMWH therapy has been reported in lung cancer patients with Trousseau's syndrome[322,323]. However, it should be noted that the ability of some LMWHs to mediate some of heparin's actions may not be equivalent[313]. Some LMWHs are not as effective at blocking L- and P-selectins, even at comparable levels of anti-factor Xa activity[313,324,325], which might be a disadvantage for the treatment of Trousseau's syndrome. There is no evidence of the efficacy of other drugs that have anti-factor Xa activity, such as danaparoid sodium, fondaparinux sodium, edoxaban tosilate hydrate, and rivaroxaban. In addition, there is no evidence of the efficacy of antiplatelet drugs, such as aspirin, dipyridamole, and cilostazol, in the treatment of Trousseau's syndrome. Some of these drugs can be taken orally, which is a greater advantage for long-term management than heparin if there is an efficacy on Trousseau's syndrome. In addition to heparin, the interruption of the inferior vena cava (IVC) with a filter can be performed to prevent life-threatening PE. Potential indications for this procedure include iliocaval thrombosis[326]. Poor survival of patients with Trousseau's syndrome has been reported. Compared with patients who did not develop a VTE, patients who developed a VTE during the course of lung cancer had decreased survival time until death[317].

CONCLUSION

The 21st century has witnessed significant progress in the understanding of some paraneoplastic syndromes associated with lung cancer, especially paraneoplastic neurological syndromes. The elucidation of the mechanisms by which these syndromes occur could lead to the development of new therapeutic strategies. Currently, treatment for these syndromes fundamentally consists of direct therapies aimed at the underlying lung cancer. In the era of molecular-targeted therapy, newly developed drugs have resulted in favorable outcomes in some cases. Remarkable progress is occurring in the development of molecular-targeted therapies for paraneoplastic syndromes.

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