Paraneoplastic syndromes: the way to an early diagnosis of lung cancer

Sindroamele paraneoplazice: posibilitatea unui diagnostic precoce în cancerul pulmonar

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Abstract

Pulmonary malignancies are the leading cause of cancer mortality around the world. The late diagnosis of lung cancer, in advanced stages, is mainly due to atypical clinical presentation. Paraneoplastic syndromes have been first described in 1825, as a group of symptoms related to a malignant disease, which are not the effect of the primary neither of the metastatic tumor. The paraneoplastic syndromes have been reported in all types of lung cancer, but more frequently in small cell lung cancer, due to its origin in neuroendocrine cell precursors. The most frequent associated syndromes described in the literature are neurological and endocrine. In most patients paraneoplastic syndromes occur prior to other symptoms of malignancy. The presence or the severity of these syndromes is not correlated with the stage of cancer. Most of the paraneoplastic syndromes disappear once the primary tumor is removed and reappear in case of cancer recurrence or metastasis. This paper is a review of paraneoplastic syndromes in lung cancer.

Keywords: *lung cancer, paraneoplastic syndrome*

Rezumat

Neoplazia pulmonară este principala cauză de deces prin cancer din întreaga lume. Diagnosticul tardiv de cancer pulmonar, în principal în stadiile avansate, se datorează unei lipse de specificitate a tabloului clinic. Sindroamele paraneoplazice au fost descrise pentru prima dată în 1825 ca un grup de simptome ce apar într-o neoplazie, fără însă a fi induse de malignitate sau de tumorile metastatice. Deși aceste sindroame au fost descrise în toate tipurile de cancer pulmonar s-a raportat o frecvență crescută a lor în cancerul pulmonar cu celule mici. Cele mai des descrise în literatură sunt sindroamele paraneoplazice ce implică sistemul endocrin sau neurologic. În unele cazuri de neoplazii aceste sindroame apar ca prime simptome. Însă prezența sau severitatea sindroamelor paraneoplazice nu a fost corelată cu stadiul maladiei. De cele mai multe ori aceste sindroame dispar sub terapie specifică neoplazică și pot reapare în caz de recidivă sau metastază. Această lucrare este un rezumat al sindroamelor paraneoplazice ce apar în cancerul pulmonar.

Cuvinte-cheie: *cancer pulmonar, sindroame paraneoplazice.*

Introduction

Pulmonary malignancies are the leading cause of cancer mortality around the world and the most common cancer worldwide since 1985[1]. Epidemiological studies have shown that the mortality rate in lung cancer is equal with prostate, breast and colon cancer combined[2]. These data are partially explained by the advanced stage at the moment of diagnosis: the reported mortality rate from the time of diagnosis is around 85-90%[3]. Even though several other risk factors have been suggested (occupational carcinogens, genetics, chronic obstructive pulmonary disease, obesity, air pollution, diet, infections), tobacco use remains the main risk factor: one in nine smokers will develop lung cancer[2].

Lung cancer has its origins in respiratory epithelium. Histopathologically there are two main types of lung cancer: small cell lung cancer (SCLC) - about 15% of cases - and non-small cell lung cancer (NSCLC), with an incidence of 85%[2]. NSCLC is divided into three major pathological subtypes: adenocarcinoma, squamos cell carcinoma and large cell carcinoma. The late diagnosis of lung cancer, in advanced stages, is mainly due to the lack of clinical findings. Sometimes, patients may seek medical advice for symptoms apparently not related to a malignancy. The appearance of paraneoplastic syndromes may lead to the diagnosis of cancer in an early stage, with early initiation of chemotherapy[4]. The paraneoplastic syndromes have been reported in all types of lung cancer, but more frequently in SCLC, due to its origin in neuroendocrine cell precursors.

Paraneoplastic syndromes represent a group of symptoms related to a malignant disease which are not the effect of the primary or of the metastatic tumor. A paraneoplastic syndrome was described for the first time in 1825 by Armand Trousseau in a patient with gastric cancer and venous thrombosis. Brown reported in 1928 the presence of Cushing syndrome in a case of small cell lung cancer, associated with hypertension and adrenal hyperplasia. Several years later, in 1957, Schwartz and Barter defined a new syndrome in two patients with lung cancer who developed hyponatremia. The correlation between SCLC and neurological paraneoplastic syndrome was mentioned the first time by Oppenheim at the end of the 19th century. In 1933, Weber and Hill described a sensory neuropathy as the most frequent clinical manifestation in oat cell carcinoma. Over the years, reports about neurological paraneoplastic involvement in lung cancer increased. In 1965 Wilkinson reported the first antineuronal antibody. But only in 1985 Graus et al gave the name of "anti-Hu immunoglobulin G antibody" to a group of proteins expressed in the neurons from central and peripheral nervous system in paraneoplastic syndromes. This antibody can be found in several malignancies, not only in SCLC: Hodgkin's disease, thymic or

testicular carcinoma, synovial sarcoma. The reports show a prevalence of 90% of anti-Hu antibody in SCLC[5].

The prevalence of paraneoplastic syndromes in lung cancer was reported as about 10%[3]. The presence or the severity of these syndromes is not correlated with the stage of cancer. In most patients paraneoplastic syndromes occur prior to any other symptoms of malignancy. Most of these syndromes disappear once the primary tumor is removed and reappear in case of recurrence or metastasis[6]. Regarding their pathophysiological mechanism, several hypotheses have been described: secretion of biologically active substances such as antibodies, hormones, enzymes, fetal proteins, cytokines either by the tumor or in response to the tumor presence (endocrine paraneoplastic syndrome) or immune cross-reactivity between tumor and normal tissues (neurological paraneoplastic syndrome)[7]. However, the presence of the these antibodies does not influence the prognosis[8].

Lung cancer may present with several types of paraneoplastic syndromes: endocrine (hypercalcemia, syndrome of inappropriate antidiuretic hormone production (SIADH) and Cushing syndrome), neurological (limbic encephalitis, Lambert-Eaton, myasthenic syndrome, peripheral neuropathy, cortical cerebellar degeneration), dermatological (dermatomyositis, hypertrophic osteoarthropathy, leukocytoclastic vasculitis), hematological (eosinophilia, granulocytosis, thrombocytosis). There are other paraneoplastic syndromes, less frequently associated with lung cancer, such as: gynecomastia, elevated levels of lutein stimulating hormone (LSH), follicle stimulating hormone (FSH), hyperthyroidism, intestinal pseudo-obstruction, necrotising myelopathy, retinopathy, glomerulonephritis, nephrotic syndrome, lactic acidosis, hypouricemia. Table 1 presents the most important paraneoplastic syndromes in lung cancer and their characteristics.

Endocrine paraneoplastic syndromes are caused by tumor production of hormones and peptides, which lead to metabolic disturbances: hypercalcemia, inappropriate antidiuretic hormone secretion, Cushing syndrome, hypoglycemia. Usually, they are diagnosed after the cancer has been discovered. The exception to this rule is Cushing syndrome. Treatment of the underlying tumor is the best strategy to control the endocrine symptoms.

Hypercalcemia is a paraneoplastic syndrome, which may occur in both solid and hematological malignancies. It is frequently observed after the patients were diagnosed with lung cancer, breast cancer or myeloma. The reported prevalence is between 20-30% and its presence suggests a poor prognosis[9]. Paraneoplastic hypercalcemia has three mechanisms: tumor secretion of parathyroid hormone-related protein secondary to activation of calcium sensing receptor (especially in squamos cell lung cancer), tumor production of calcitriol (lymphoma), osteolytic metastases (breast cancer, myeloma)[9,10]. The clinical features depend on the severity and rapidity of onset. Patients may experience nausea, vomiting, abdominal pain, lethargy, renal failure and coma. The diagnosis is confirmed by laboratory tests: high serum levels of ionized calcium, low to normal parathyroid hormone (PTH) level, high PTH-related protein (PTHrP) concentration. The optimal approach of hypercalcemia remains the treatment of underlying cancer[7]. The treatment should be revised and drugs that contribute to hypercalcemia should be stopped (thiazide diuretics, lithium, calcium supplements). Specific treatment includes intravenous bisposphonates. Usually, serum calcium levels will return to normal within 7 days and will be controlled for 3 weeks. The main adverse events include mild, asymptomatic hypocalcemia and osteonecrosis. In patients with chronic renal failure the alternative is calcitonine administration, which inhibits bone resorption and increases renal excretion of calcium[9]. In persistent hypercalcemia, fluid repletion with normal saline solution followed by loop diuretics may be useful.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by hypoosmotic, euvolemic hyponatremia, with an independent poor prognosis[11]. It is found in 1-2% of patients with cancer, but is more frequent in SCLC: 10-45%[7]. SIADH appears secondary to excess production of antidiuretic hormone (ADH) and atrial natriuretic peptide by the neoplastic cells. The reduction of free water clearance while maintaining the extracellular fluid is the main mechanism of SIADH. Despite the excess of ADH is found in 70% of patients with lung cancer, only 5% of them have SIADH[7]. The presence of euvolemic status is critical for diagnosis, because hyponatremia accompanied by hypovolemia is found in gastrointestinal loses, diuretic treatment, adrenal insufficiency and cerebral salt wasting[12].

Clinical presentation depends on the degree of hyponatremia and includes headache, memory loss, confusion, seizures and coma. The diagnosis of SIADH is confirmed by laboratory tests (serum sodium < 125 mEq/l, urinary sodium > 40 mmol/l, urine osmolality > 100 mOsm/kg).

Control of the underlying cancer is the best treatment for SIADH. Symptoms improve after hyponatremia correction with hypertonic saline fluids (3% concentration). The rate of administration depends on the rapidity of the onset of hyponatremia. In acute cases, less than 48 hours, correction by 1-2mmol/l/hour with a maximum of 8-10mmol/l/day is recommended; in chronic hyponatremia, the recommended rate of correction is 0.5-1 mmol/l/hour. If rapid correction, central pontine myelinolysis due to brain dehydration may appear. Pharmacological treatments such as demeclocycline, or vasopressin receptor antagonists may be used in case of failure of hypertonic fluids[7, 13].

Another endocrine paraneoplastic syndrome is represented by **hypercorticism or Cushing syndrome.** 5-10% of all Cushing syndromes are paraneoplastic from which about 50-60% are due to neuroendocrine lung tumors such as SCLC and carcinoids[7,14]. Hypercorticism appears by the tumor secretion of adrenocorticotropic hormone (ADH) or corticotropin-releasing factor. This translates into an increased production and release of cortisol by the adrenal glands. Clinical signs consist of weakness, muscle wasting, confusion, psychosis, hyperglycemia, hypertension, hypokalemia. The laboratory tests show a cortisol level >29 mcg/dl, urinary free cortisol >47 mcg/24h, ADH at midnight >100 g/l. The suppression test, which is negative in paraneoplastic Cushing syndrome, is useful for the differential diagnosis. The test consists of the administration of 2 mg

Table 1 The most important paraneoplastic syndromes in lung cancer and their characteristics.

Syndrome	Mechanism	Diagnosis	Characteristics	Specific treatment	Prognosis
Hypercalcemia	TS	After	•Caincreased •PTH normal	Biphosphonates	Poor
SIADH	TS	Before	•Euvolemia •pNa<125mEq/L •uNa>40mmol/L •uOsm>100mOsm/kg	Hypertonic saline fluids	-
Cushing	TS	After	•pCortisol>29mcg/dL •uCortisol>47mcg	•ketoconazole •octeotride•etomidate •mifepristone•adrenale ctomy	Infections
Dermatomyositis	-	Before	•CK •EMG •Biopsy	CS	Residual motor impairement
Hypertrophic osteoarthropathy	-	Before	Scintigraphy	•Bisphosphonates •NSAID •RT	-
Leukocytoclastic vasculitis	Ag	Before	Biopsy	•CS •Colchicine •Dapsone •MTX	-
Paraneoplastic neuromyotonia	Ag	Before	EMG	•Phenytoin •Carbamazepine •IMT	-
Eosinophilia	-	After	-	CS	Tumor recurrence
Granulocytosis	TS	After	-	-	-
Thrombocytosis	TS	After	-	-	Poor
Trousseau syndrome	TS	After/ Before	-	LTA	Poor
Limbicencephalitis	Ag	Before	•MRI •LP	-	-
Cerebellar degeneration	Ag	Before	-	•CS •IMT •PLF	Poor
Opsoclonus- myoclonus	Ag	-	-	-	-
Lambert-Eaton	Ag	Before	EMG	IMT	-
Peripheral hyperexcitability	Ag	Before	EMG	•CS •IMT •PLF	-
Neuropathy	Ag	-	•EMG •LP	-	-
Peripheral nerve vasculitis	Ag	-	-	-	-

Legend: ADK- adenocarcinoma; Ag-antigen; NSAID - nonsteroid anti-inflammatory drugs; CK- creatine kinase; CS-corticotherapy; EMG-electromyography; LTA-long term anticoagulation; LP-lumbar puncture; IMT-immunotherapy; MRI-magnetic resonanceimaging; MTX-methotrexate; pCortisol-plasmatic cortisol; PLF-plasmapheresis; pNa-plasmatic Na; RT-radiotherapy; TS-tumor secretion; SIADH-syndrome of inappropriate antidiuretic hormone secretion; uNa- urinary Na; uOsm- urine osmolality; uCortisol- urinary free cortisol/ 24h

of dexamethasone every 6 hours for 72 hours, with the measurement of urine 17-hydroxycorticosteroid at 9 am and at midnight, day 2 and 3 after the test. A positive test means a reduction by 50% in 17-hydrocorticosteroid level.

The control of the underlying tumor is the best therapy for the Cushing paraneoplastic syndrome, as in all paraneoplastic syndromes. Specific treatment includes inhibitors of steroid production (ketoconazole, mitotane, metyaprone, aminoglutethimide), blockers of ADH release (octeotride), inhibitors of steroid synthesis (etomidate), blockers of glucocorticoid receptor (mifepristone). If the patient remains symptomatic despite medical treatment, adrenalectomy may be considered. Symptomatic treatment is represented by antihypertensive agents, with a careful ionogram monitoring. Despite appropriate treatment, symptoms may reappear with tumor progression[7,14]. It has been suggested that achieving control of cortisol levels before starting chemotherapy may reduce mortality rates [14].

Dermatological paraneoplastic syndromes develop prior to the diagnosis of cancer and may present as dermatomyositis, hypertrophic osteoarthropathy, leukocytoclastic vasculitis, pemphigus (B-cell lymphoproliferative

disorders), Sweet syndrome (hematologic malignancy, gastrointestinal and breast cancer), acanthosis nigricans (frequently in gastric carcinoma) and erythroderma (leukemia, T-cell lymphoma).

Between 10-25% of **dermatomyositis** cases are paraneoplastic[7]. The most frequent malignancies associated with this syndrome are lung, breast, ovarian and prostate cancer. Clinical features may include rash and papules, which mimic psoriasis, and muscle weakness. Paraclinical tests show an elevated level of creatinekinase and electromyographic changes. Muscle biopsy reveals perivascular inflammation, with a mixture of B and T cells, and perifascicular atrophy. Oral corticotherapy and immune-modulating therapy have been used, with limited results. These syndromes are less responsive to specific therapy compared to those of non paraneoplastic origin[15]. Tumor specific treatment improves symptoms, but up to 30% of patients may have residual motor impairment[7].

Another dermatological paraneoplastic disorder called **hypertrophic osteoarthropathy** has been reported in patients with squamous cell lung cancer or adenocarcinoma[16]. About 90% of the cases are paraneoplastic[7]. The syndrome is more common in women and it is characterized by painful symmetrical artropathy with periostal new bone formation. Scintigraphy shows symmetric and concentrated tracer uptake in the affected bones. Treatment options include biphosphonates, non-steroid anti-inflammatory drugs, opioids, palliative radiation and, of course, treatment of the underlying tumor.

Leukocytoclastic vasculitis is a paraneoplastic syndrome seen in both solid tumors (lung, gastrointestinal, urinary cancer) and hematologic malignancies. This syndrome is less frequently associated with cancer comparing to hypertrophic osteoarthropathy, so screening for malignancies in patients without other signs is not recommended. The mechanism of leukocytoclastic vasculitis involves the presence of circulating tumor-associated antigens. Clinical symptoms precede malignancy diagnosis and consist of purpura in lower extremities accompanied by pain, burning and pruritus. Renal or gastrointestinal symptoms are rarely seen[17]. Symptomatic treatment for mild to moderate syndrome consists of colchicine, Dapsone and oral cortosteroids. In case of resistant disease: methotrexat or azathioprine may be considered. As in all paraneoplastic syndromes, the malignancy treatment remains the cornerstone.

Paraneoplastic neuromyotonia is associated with SCLC, thymoma and Hodgkin lymphoma. In some cases, the presence of antibodies was reported: contactin-associated protein-2, leucineglioma inactivated 1[18]. Clinical presentation includes muscle stiffness caused by continuous activity and delayed relaxation, motor weakness, sweating and intestinal pseudo-obstruction. The association with central nervous system symptoms is called Morvan's syndrome and is characterized by confusion, memory loss, hallucinations and seizures. Diagnosis is confirmed by electrophysiological studies, which reveal discharges at high frequency and irregular intervals, even during sleep or general anesthesia. Symptomatic treatment includes phenytoin, carbamazepine, diazepam, plasma exchange or immunotherapy.

Hematological paraneoplastic syndromes are usually diagnosed in advanced stages. They are clinically asymptomatic and rarely require specific therapy. Anomalies may include: eosinophilia, granulocytosis, thrombocytosis and red cell aplasia.

Paraneoplastic eosinophilia appears secondary to tumor production of eosinophil growth factor, interleukin (IL3, IL5, GM-CSF). It is frequently associated with lymphomas and leukemia, but it can also be identified in lung, gastrointestinal and gynecological cancers. Also, secondary eosinophilia may be found in allergic reactions, parasitic infections, collagen and vascular disease. Usually, this syndrome is asymptomatic, only occasionally may manifest with wheezing and dyspnea. These symptoms respond to corticosteroid therapy. The syndrome disappears with successful treatment of the underlying tumor and its recurrence may be a sign for tumor recurrence[7].

Paraneoplastic granulocytosis is seen in large cell lung cancer as well as in gastrointestinal, brain, breast, renal and gynecological malignancies. The physiopathological mechanism includes both tumor production of colony-stimulating factors and bone marrow involvement by tumor[19, 20]. The syndrome is clinically silent. Granulocytosis may appear in many clinical circumstances, the diagnosis of paraneoplastic granulocitosis being an exclusion diagnosis. Leukapharesis is not necessary in this syndrome because deformable neutrophils are unlikely to cause leukostasis below $250x10^9/l$[7].

Paraneoplastic thrombocytosis appears in malignancies such as lung, breast, gastrointestinal and gynecologic cancers. It occurs due to tumor production of cytokines such as IL-6[7]. Paraneoplastic thrombocytosis is an asymptomatic syndrome, neither bleeding or clotting abnormalities are found. There is no indication for specific treatment. The presence of the syndrome is associated with advanced disease and poor prognosis[21,22].

Another hematological paraneoplastic syndrome, known as **Trousseau syndrome**, is usually associated with pulmonary or pancreatic adenocarcinoma. Clinically, it translates into venous thrombosis and hypercoagulability. Circulating cell factor containing microvesicles secreted by the tumor have been incriminated in producing this hypercoagulable state. The paraneoplastic thrombophlebitis is migratory. Long term anticoagulants should be considered[7,23].

The presence of a **paraneoplastic neurological syndrome** is rarely seen in cancer patients (less than 1%), but the prevalence increases up to 5% of lung cancer, especially in SCLC[7]. This syndrome is due to the appearance of onconeural antibodies which result from an immune reaction between tumor cells and the nervous system. These antibodies are detectable in the serum of patients with cancer and paraneoplastic syndromes, but also in patients without neurological symptoms and even in patients without malignancies. Due to the lack of sensitivity and specificity of onconeural antibodies, the paraneoplastic neurological syndrome is an exclusion diagnosis.

Given the difficulties in the diagnosis of neurological paraneoplastic syndrome, international criteria have been developed, which divide the diagnosis in "definite" and "possible". Definite diagnostic of neurological paraneoplastic syndromes include four possibilities: a) a neurological syndrome frequently associated with cancer (limbic encephalitis, cerebellar degeneration, opsoclonus-myoclonus, neuropathy, Lambert-Eaton syndrome) that will develop malignancy within five years; b) a non-classical neurological syndrome which improves with cancer therapy without concomitant immunotherapy; c) a non-classical neurological syndrome with positive antibodies and malignancy diagnosed within five years; d) a neurological syndrome with "well-characterized" antibodies (anti-Hu, anti-CV2, anti-Ri, anti-Yo, anti-Tr, anti-Ma2) without cancer diagnosis. A possible diagnosis of neurological paraneoplastic syndromes include three categories: a) a classical neurological syndrome without antibodies or cancer, but with high risk of underlying tumor; b) a neurological syndrome with non-classical antibodies and no cancer; c) a non-classical neurological syndrome without antibodies and malignancy proven within two years[24].

Differential diagnosis is made with electrolyte imbalances, an infectious or toxic etiology, rhythm disturbances, meningitis, cerebral metastases or overdose of morphine. Usually, symptoms appear prior to cancer diagnosis. If there is suspicion of a neurological paraneoplastic syndrome, screening for an underlying malignancy should be done every 3 to 6 months, for 2 to 3 years[7]. Successful cancer treatment does not always improve neurological symptoms. Immunosuppressive therapy may be considered, with variable results. Regarding prognosis, the diagnosis of neurological paraneoplastic syndrome may lead to the diagnosis of cancer in an early stage. On the other hand, this syndrome may cause irreversible damages to the nervous system, with increased mortality[7, 8,25].

The clinical presentation of neurological paraneoplastic syndrome is variable, it may affect the central nervous system (limbic encephalitis, cerebellar degeneration), the neuromuscular junction (Lambert-Eaton, myasthenic syndrome) or peripheral nervous system (subacute sensory neuropathy). The Lambert-Eaton syndrome is most commonly seen in SCLC and the myasthenia Gravis in thymoma[8].

Paraneoplastic limbic encephalitis may appear in different types of cancer, such as Hodgkin's lymphoma, thymoma and immature teratoma, but is mainly seen in SCLC (40%)[26]. Symptoms usually appear 3-5 months prior to cancer diagnosis and include amnesia, disorientation, hallucinations, anxiety, and even seizures. Magnetic resonance imaging (MRI), electroencephalogram and lumbar puncture are useful for diagnosis. Two types of antibodies have been identified in about 60% of patients[8]. The onconeural antibodies target intracellular antigens and are the expression of the underlying tumor. Anti-Hu antibodies are frequent in SCLC and can be related to other neurological paraneoplastic syndromes. Other onconeural antibodies are: anti-Ma2, anti-CV2/CRMP5, anti-amphihysin. Another type of antibodies incriminated are directed towards the surface receptors: voltage-gated potassium channel, anti-N-methyl-D-aspartate. Symptoms are reduced by cancer specific therapy. Although it is an immune-mediated syndrome, there are no solid proofs about immune therapy benefits[7].

Paraneoplastic cerebellar degeneration is a subacute dysfunction of the cerebellum and occurs in SCLC, Hodgkin's disease, breast and ovarian cancer. Clinical signs are ataxia, dysarthria and nystagmus. It has a poor outcome, the patient is tied to his bed within three months after diagnosis. The MRI is useful in advanced stages, when it shows cerebellar atrophy. The anti-Hu antibodies are present in 13-20% of cases, the anti CV2/CRMP5 antibodies appear mainly in males and are associated with neuropathy, anti-Tr antibodies usually disappear after treatment and anti-RI antibodies are found in patients with both cerebellar ataxia and opsoclonus-myoclonus[8,26]. The absence of these antibodies does not exclude the diagnosis. The presence of anti-Hu antibodies is linked with a worse prognosis. The treatment consists of the management of the underlying cancer. There have been few reports of a favorable evolution after using immunoglobulin, steroids and plasmapheresis. Symptoms may be controlled by neurological rehabilitation and antiepileptic drugs.

Paraneoplastic opsoclonus-myoclonus differs from most paraneoplastic syndromes because clinical signs are remitting and relapsing. It is often accompanied by ataxia, limb myoclonus and encephalopathy. It is seen in children with neuroblastoma and in adults with lung, breast or ovary cancer. The diagnosis in adults depends on scanners that can prove the presence of the tumor. Symptoms as nystagmus or oscillopsia may benefit from anti-epileptic drugs. There are not randomized trials to prove the utility of plasma exchange, immunoglobulin, steroids, cyclophosphamide or azathioprine[7,26].

Lambert-Eaton syndrome is defined as a muscle weakness which starts in the legs and spreads to all skeletal muscle and rarely leads to the need for artificial respiration. Almost half of patients with Lambert-Eaton syndrome will be diagnosed with a SCLC[26]. Symptoms are usually mild and include ptosis, diplopia and autonomic dysfunction such as dry mouth and eyes, constipation, impotence and ortostatic hypotension. In about 10% of SCLC cases with Lambert-Eaton syndrome, paraneoplastic cerebellar degeneration is also associated. Electromyographic recording may be used to diagnose reduced potentials. Regarding antibodies, the presence of anti P/Q type VGCC antibodies was reported in 85% of cases, HLAB8 antibodies in 69% and SOX antibodies in 64%[26]. After specific therapy for SCLC the symptoms regress in 6-12 months[26]. Symptomatic treatment consists of 3,4-diaminopyridine.

Paraneoplastic peripheral nerve hyperexcitability syndrome is less frequently associated with SCLC (only 7%) and can precede the diagnosis of cancer up to 4 years[26]. It is considered an autoimmune syndrome, VGKC antibodies are found in 35% of the cases, up to 80% in patients with tymoma[26]. Clinical features are twitching, painful cramps and weakness due to spontaneous muscle over activity. The electromyography is used for differential diagnosis. The scan is helpful for identifying the tumor. Treatment consists in chemotherapy for SCLC and antiepileptic drugs. Immunotherapy, such as plasma exchange, immune modulation and Prednisolone may induce clinical improvement.

The peripheral nervous system is also involved in paraneoplastic syndrome. Usually this neuropathy has a poor response to immune therapy or treatment of the underlying tumor. **Subacute sensory neuropathy** is predominantly expressed in lung cancer. It is produced by ganglion degeneration and has a subacute onset with 4-5 months before the diagnosis[26]. Symptoms involve in the first phase the upper limbs, but their extent varies. Clinical onset is represented by the loss of vibratory sensation, followed by paresthesias, pain, acute hyporeflexia, ataxia, digestive pseudo-obstruction. The spinal fluid analysis shows high protein concentration. Electromyography reveals altered velocities and nerve biopsy is necessary for differential diagnosis of neuropathy due to vasculitis. Anti-Hu antibodies are also present with a sensitivity of 80%[27]. Anti CV2/CRMP5 antibodies may be also present in motor neuropathy.

Mixed neuropathy may appear in several malignancies, including lung cancer, and it is produced by myelitis. Chronic sensorimotor neuropathy is frequently seen in patients with solid tumors, in about 10-15% of the cases[27]. The clinical presentation may include the predominance of either motor or sensory symptoms: paraplegia, areflexia and loss of sphincter control. Electromyography proves an axonal neuropathy with possible decreased conduction velocities. The differential diagnosis includes side effects of chemotherapy, diabetes, alcoholism and vitamin B12 deficiency.

Paraneoplastic autonomic neuropathy is associated especially with SCLC, but it is also seen in other malignancies such as pancreatic or thyroid cancers, Hodgkin lymphoma and carcinoid tumors of the lung. It may be accompanied by other syndromes, such as encephalomyelitis or sensory neuropathy. In patients with SCLC and paraneoplastic autonomic neuropathy, anti-Hu antibodies are frequently detected[26,27]. Clinical presentation includes hypothermia, hypoventilation, sleep apnea, cardiac arrhythmias and gastroparesis. There are reports that immunosuppressive treatment associated with corticotherapy and mycophenolatemofetil may have good results[7, 26].

Paraneoplastic peripheral nerve vasculitis has been reported in SCLC, prostate and endometrial cancer, Hodgkin and non-Hodgkin lymphoma[27]. Patients present with painful asymmetrical sensitive and motor deficits. Diagnosis is confirmed by biopsy, which reveals mononuclear infiltrate without necrosis or atypical cells.

Conclusions.

Despite the availability of new diagnostic techniques and development of biological and surgical treatment, lung malignancy mortality remains the leading cause of cancer related deaths since 1985. Clinical presentation of patients with this malignancy is usually poor and nonspecific. The presence of "atypical" symptoms of a lung cancer should not exclude its possibility. SCLC is the most frequent histological type associated with paraneoplastic syndromes. The most frequent paraneoplastic syndromes described in the literature are neurological and endocrine syndromes. Clinical onset of paraneoplastic syndromes may be prior to the cancer diagnosis or may develop as a complication of disease progression. Nevertheless, the prognosis is influenced by the treatment of the underlying tumor. The recurrence of paraneoplastic symptoms signals tumor progression. ■

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