International Journal of Research and Review
Vol. 10; Issue: 7; July 2023
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Paraneoplastic Syndromes in Small Cell Lung Cancer: A Narrative Review

Archana Rajan[1], Abhisek Sahoo[2]

[1]Department of Medicine, [2]Department of Physiology,
All India Institute of Medical Sciences, New Delhi, India

Corresponding Author: Archana Rajan

DOI: https://doi.org/10.52403/ijrr.20230778

ABSTRACT

Paraneoplastic syndromes are commonly associated with lung cancer, particularly small-cell lung cancer. These syndromes often occur before the cancer is diagnosed or in the early stages of the disease. However, they can also occur at the time of metastasis. Through this article, we want to focus on the epidemiology, pathophysiology, symptoms, and current treatment approaches for the most frequent paraneoplastic syndromes seen in patients with small-cell lung cancer. Recent advancements have improved our understanding of these syndromes and provided better diagnostic and therapeutic options. Being aware of paraneoplastic syndromes in small-cell lung cancer can lead to earlier detection and diagnosis, potentially improving the overall prognosis and survival rates for patients. Further studies are needed to investigate effective strategies in patients with paraneoplastic neurological disorders.

Keywords: Paraneoplastic syndrome, small cell lung cancer, hypercalcemia

INTRODUCTION

First used in the year 1940 the term paraneoplastic syndrome refers to a clinical or laboratory manifestation caused due to an immune reaction or due to the remote effect of cancer cells not due to its mass effects. Some paraneoplastic syndrome may herald the appearance of malignancy in the body enabling an early diagnosis while some appear at the time of diagnosis of the primary tumor itself or with metastasis hence, there might be no relation between the severity of paraneoplastic symptoms and signs to the stage of the underlying cancer [1]. Recent advancements have improved our understanding of these syndromes and provided better diagnostic and therapeutic options. Being aware of paraneoplastic syndromes in small-cell lung cancer can lead to earlier detection and diagnosis, potentially improving the overall prognosis and survival rates for patients.

ETIOLOGY

Small cell cancer of the lung is the most common cancer associated with paraneoplastic syndromes, probably because of its neuroectodermal origin often producing biologically active reported mOS of 15-20 months when localized (L-SCLC) and 9-11 months when extensive (E-SCLC) [2]. Other neoplasms commonly associated are carcinomas of the breast, ovary, other adenocarcinomas, and lymphoproliferative diseases (especially Hodgkin's disease and thymoma.

Paraneoplastic syndromes with small cell lung cancer
Cutaneous manifestation
Polymyositis/Dermatomyositis
Neurologic syndromes
Autonomic neuropathy
Cerebellar degeneration
Lambert-Eaton syndrome
Limbic encephalitis
Opsoclonus – myoclonus ataxia
Retinal blindness
Stiff person syndrome
Subacute sensory neuropathy
Endocrine syndrome
Acromegaly
Cushing's syndrome
Hypercalcemia
SIADH

Table 1- Various paraneoplastic syndromes associated with small-cell lung cancer.
Abbreviations: SIADH-syndrome of inappropriate antidiuretic hormone secretion

EPIDEMIOLOGY

Around 8% of individuals diagnosed with cancer are believed to experience paraneoplastic syndrome, and it is expected that this prevalence will rise due to advancements in diagnostic methods and the fact that people are living longer nowadays.

PATHOPHYSIOLOGY

The pathogenesis of paraneoplastic syndromes involves complex mechanisms that are not fully understood. However, there are several proposed theories to explain their development-

Remote effects of tumors: Paraneoplastic syndromes are characterized by symptoms that occur at sites distant from the primary tumor. It is believed that tumors can produce hormones, cytokines, or other bioactive substances that are released into the bloodstream and affect various organs or tissues. These substances can interact with specific receptors or disrupt normal cellular functions, leading to the development of paraneoplastic syndromes. Cytokines such as IL-1, IL-3, IL-6, prostaglandins, TGF-α, TNF-α (lymphotoxin), and TNF-β (cachectin) are created by cancerous cells and can lead to elevated levels of calcium in the blood by stimulating osteoclasts.

Autoimmunity: In some cases, paraneoplastic syndromes are thought to result from an immune response against tumor antigens. The immune system recognizes antigens expressed by both the tumor cells and normal cells, leading to an autoimmune attack on the normal tissues. This autoimmune response can cause inflammation and tissue damage, resulting in the associated paraneoplastic syndrome.

Cross-reactivity: Tumor cells can express antigens that are similar to antigens found in normal tissues. This similarity can lead to an immune response that targets both the tumor and normal tissues, resulting in paraneoplastic syndromes. For example, antibodies produced against tumor antigens may also react with antigens expressed in the nervous system, leading to neurological paraneoplastic syndromes.

Ectopic hormone production: Some tumors can produce hormones or hormone-like substances that are not typically synthesized by the tissue from which the tumor originated. The ectopic production of hormones can lead to hormonal imbalances and the development of paraneoplastic syndromes. Examples include ectopic production of adrenocorticotropic hormone (ACTH) by small cell lung cancer, causing Cushing's syndrome, or production of parathyroid hormone-related peptide (PTHrP) by certain cancers, leading to hypercalcemia.

It is important to note that the pathogenesis of paraneoplastic syndromes can vary depending on the specific syndrome and

underlying tumor type. Therefore, understanding the exact mechanisms involved in each case requires further research and investigation.

CUTANEOUS MANIFESTATIONS

Dermatomyositis

Dermatomyositis is an inflammatory myopathy often associated with multiple skin lesions before the onset of proximal muscle weakness and can sometimes present with characteristic skin rashes without any muscle weakness. Around 10-25% [3,4] of cases are associated with malignancy, hence expedited age-appropriate examinations and tests to screen for malignancy are advised in all patients.

Commonly associated malignancies are lung cancer, breast cancer, non-Hodgkin lymphoma, ovarian and prostate cancer. So, screening can be done with CT chest, abdomen, and pelvis.

Skin manifestations include that are pathognomonic- Heliotrope rash which is oedema and purple discolouration of eyelids and Gottron papules, a scaly eruption over the phalangeal joints while other not pathognomonic lesions include violaceous erythema over the anterior chest called V sign while upper back and shoulder is called shawl sign, malar rash, violaceous erythema over extensor surfaces.

One of the known risk factors for the development of malignancy-associated dermatomyositis is positivity for anti–transcription intermediary factor 1-γ (TIF1-γ).TIF1- is a transcription factor that regulates cellular proliferation and is thought to be a tumor suppressor due to its capacity to ubiquitinate or compete with Smad3 or 4. TIF1- inactivation, mutation, or downregulation leads to tumorigenesis and metastasis [5].

Diagnosis of dermatomyositis can be made through increased levels of creatine phosphokinase (which can be used to monitor treatment progress) AST, ALT, LDH and aldolase can be raised, and distinctive findings on electromyography (myopathic pattern), and muscle biopsy results showing a perivascular inflammatory infiltrate consisting of both B- and T-cells, as well as muscle fibre atrophy surrounding the fascicles [6].

Treatment

In most cases, successful tumor-directed therapy will also ameliorate symptoms; however, up to one-third of patients will have a substantial residual motor impairment and requires multidisciplinary management [6] such as-

- Physical Therapy: Physical therapy plays a crucial role in managing muscle weakness and improving overall function in dermatomyositis. A physical therapist can help design an exercise program tailored to individual needs and abilities to improve strength, range of motion, and overall mobility.
- Topical corticosteroids, such as topical creams or ointments, alleviate skin manifestations like rashes and skin inflammation. Sun protection measures, including sunscreen and protective clothing, are also needed, as photosensitivity is common in dermatomyositis.
- Corticosteroids: Corticosteroids, such as prednisone, are the mainstay of treatment and are commonly prescribed to reduce inflammation and manage muscle weakness and skin manifestations associated with dermatomyositis. High doses of corticosteroids may be initially required, followed by a gradual tapering of the dose once the symptoms are under control.
- Immunosuppressants: Additional immunosuppressive medications may be sometimes required for example methotrexate, azathioprine, mycophenolate mofetil, or rituximab. These medications work by suppressing the overactive immune response that is seen in dermatomyositis.
- Intravenous Immunoglobulin (IVIG): IVIG therapy involves infusing purified antibodies into the bloodstream and has

shown effectiveness in managing dermatomyositis symptoms. IVIG may be considered when corticosteroids and immunosuppressive medications are not providing adequate relief or if there are contraindications to their use.

- Unlike dermatomyositis, polymyositis is an inflammatory muscle disorder that typically does not present with any dermatological symptoms and is infrequently associated with malignancy.

ENDOCRINE SYNDROME

Cushing's syndrome

It is a rare but important Paraneoplastic syndrome that consists of a collection of symptoms and signs caused by prolonged exposure to high levels of cortisol (a hormone produced by the adrenal glands). In the context of SCLC, Cushing's syndrome can occur due to the secretion of adrenocorticotropic hormone (ACTH) or adrenocorticotropin-releasing hormone (CRH) by the tumor, which stimulates excessive cortisol production by the adrenal glands.

Around 5% to 10% of Cushing syndrome cases, are associated with paraneoplastic conditions [6]. Among these paraneoplastic cases, approximately 50% to 60% are attributed to neuroendocrine lung tumors, including small cell lung cancer and bronchial carcinoids[6–8].

The clinical manifestations of ectopic Cushing syndrome range from central obesity (accumulation of fat in the trunk and face), moon face (round and swollen face), buffalo hump (fat accumulation at the base of the neck), thinning of the skin with easy bruisability, purple striae (stretch marks), facial plethora, muscle weakness, hypertension, glucose intolerance or diabetes, osteoporosis, and psychological disturbances. Hypokalemia with metabolic alkalosis is almost always present in ECS patients, and the majority of cases also exhibit hyperglycemia. However, ECS associated with small cell lung cancer (SCLC) rarely presents with all the classic signs of Cushing syndrome (CS) due to the short duration of exposure to excessive adrenocorticotropic hormone (ACTH) due to the aggressive nature of SCLC and its presence is often associated with poor prognosis.

Diagnosis of Cushing's syndrome: If a patient with lung cancer displays clinical features of Cushing's syndrome (CS), it is important to rule out iatrogenic causes, such as the use of exogenous glucocorticoids. The Endocrine Society's clinical practice guidelines recommend initial diagnostic tests with high accuracy for CS, based on patient suitability. These tests include- measuring 24-hour urinary free cortisol on at least two occasions (if levels are above the normal range), measuring late-night salivary cortisol (between 11:00 PM and midnight) on two occasions (if levels are greater than 145 ng/dL), and performing the 1-mg overnight dexamethasone suppression test (administering dexamethasone at 11:00 PM or midnight and measuring blood cortisol at 8:00 AM or 9:00 AM, with a concentration above 1.8 μg/dL indicating abnormal results), or in certain cases, the 2-mg 48-hour dexamethasone suppression test. If any of these tests yield abnormal results, further evaluation, including repeat testing or additional tests such as serum midnight cortisol or dexamethasone-corticotropin-releasing hormone (CRH) test. The high-dose (8 mg) dexamethasone test, with a cortisol suppression of over 50% in urinary or serum measurements, is indicative of Cushing's disease, showing a sensitivity of 84%-89%. Computed tomography (CT) scanning is valuable for identifying ectopic sources of cortisol, Octreoscan generally provides functional data but may not detect sources undetectable on CT scans [9].

The primary treatment goal in Cushing's syndrome associated with SCLC is to address the underlying cancer. This usually involves a combination of chemotherapy, radiation therapy, and surgical intervention, depending on the stage and characteristics

of the tumor. By successfully treating the SCLC, the excessive production of ACTH or CRH is typically halted, leading to a reduction in cortisol levels [10].

In some cases, symptomatic relief for Cushing's syndrome may be necessary, particularly if the symptoms are severe or persist despite cancer treatment. This may involve the use of medications to inhibit cortisol synthesis (e.g., ketoconazole 600-1200 mg oral -it has best tolerance, metyrapone-1 g orally, less commonly etomidate 0.3 mg/kg/h IV), block cortisol receptors (e.g., mifepristone 10-20 mg/kg/day orally), or surgically remove the adrenal glands (adrenalectomy). Antihypertensive agents and diuretics, with careful monitoring of serum potassium, may also be used to control symptoms[10].

Hypercalcemia of malignancy

Hypercalcemia associated with small cell lung cancer (SCLC) is relatively rare. Small cell lung cancer cells can produce PTHrP, which mimics the action of parathyroid hormone (PTH) and increases calcium levels. PTHrP acts on the same receptors as PTH, promoting bone resorption, enhancing renal tubular calcium reabsorption, and increasing intestinal calcium absorption [11].

Clinical presentation can be due to underlying lung malignancy like cough, hemoptysis, shortness of breath, weight loss, Horner's syndrome or due to hypercalcemia such as fatigue, weakness, confusion, constipation, nausea, vomiting, increased thirst, frequent urination, kidney stones, hypertension, bradycardia and altered mental status. The severity of symptoms may vary depending on the degree of hypercalcemia [12].

Diagnosis involves measuring serum calcium levels, mild- 10.5-11.9 mg/dL; moderate 12.0-13.9 mg/dL; severe ≥14.0 mg/dL. Other laboratory tests, such as PTH levels -Low to a normal level, usually 10-20 pg/ml and PTHrP levels are elevated. These can help confirm the diagnosis and differentiate between primary hyperparathyroidism and hypercalcemia of malignancy.

Management of hypercalcemia in small-cell lung cancer focuses on both controlling the symptoms and treating the underlying cancer. Treatment options include-Treating the underlying small cell lung cancer is essential to reduce PTHrP production. This may involve chemotherapy, radiation therapy, targeted therapies, or a combination depending on the stage and characteristics of the tumor [11,13].

- Hydration: Intravenous fluid-Normal saline, 200-500 mL/h is administered to promote urine production and increase calcium excretion through the kidneys. Routine use of loop diuretics is not recommended for all patients with hypercalcemia, despite their ability to inhibit renal calcium reabsorption. However, in certain cases, after ensuring adequate fluid replenishment to prevent dehydration and worsening hypercalcemia, loop diuretics, for example, furosemide 20-40 mg IV may be considered as an additional treatment option.
- Bisphosphonates: Medications like zoledronic acid (4 mg IV) or pamidronate (60-90 mg IV) are commonly used to inhibit bone resorption and lower calcium levels. However, these need to be used with caution in patients with renal failure. Serum calcium levels will decline within 2 to 4 days, reach a nadir between 4 and 7 days after infusion, and remain suppressed for up to 3 weeks.
- Calcitonin: Calcitonin can be administered to temporarily lower calcium levels by inhibiting bone resorption at doses of 4-8 IU/kg SC or IM every 12 h, also associated with calciphylaxis but safe in renal failure.
- Glucocorticoids: In some cases, glucocorticoids for example-prednisolone 40-100 mg/d orally (for lymphoma, myeloma) may be

prescribed to suppress PTHrP production and lower calcium levels.

- Haemodialysis

Regular monitoring of serum calcium levels, hydration status, kidney function, and other relevant parameters is essential. Supportive care measures, such as pain management and addressing other symptoms, are also crucial in improving the patient's overall well-being.

SIADH-Syndrome of inappropriate antidiuretic hormone secretion

Small cell lung cancer cells can produce and release antidiuretic hormone (ADH), also known as vasopressin or arginine vasopressin (AVP). The excessive release of ADH leads to unregulated water reabsorption in the kidneys, resulting in dilutional hyponatremia and the characteristic features of SIADH. Patients with SCLC with hyponatremia had shorter survival times than patients with normal serum sodium levels[14,15].

SIADH associated with small cell lung cancer presents with hyponatremia (low serum sodium levels) due to water retention. Symptoms may include nausea, vomiting, headache, confusion, seizures, muscle cramps, gait disturbances, anorexia and in severe cases, respiratory distress, or coma.

SIADH results in euvolemic hyponatremia. Both clinical and laboratory indicators can help determine the volume status. A euvolemic state is supported by the absence of changes in vital signs upon standing, absence of oedema, normal central venous pressure, serum uric acid concentration below 4 mg/dL, and blood urea nitrogen level below 10 mg/dL. In cases of euvolemic hyponatremia, a urinary sodium level exceeding 40 mmol/L or urine osmolality higher than 100 mOsm/kg of water suggests a diagnosis of SIADH. Other causes of hyponatremia, such as adrenal insufficiency, hypothyroidism, and renal dysfunction, should be ruled out. On the other hand, hyponatremia and elevated urinary sodium or osmolality in a person with volume depletion indicate appropriate ADH secretion and response to volume replenishment.

If symptomatic hyponatremia develops within 48 hours, the serum sodium level can be increased by 1 to 2 mmol/L per hour, but typically not more than 8 to 10 mmol/L within the first 24 hours of treatment. In cases of chronic hyponatremia, the brain adapts by producing its osmoles to prevent intracellular swelling. Swift correction of hyponatremia can result in water leaving the brain, leading to brain dehydration and the development of central pontine and extrapontine myelinolysis. This condition manifests as lethargy, dysarthria, spastic quadriparesis, and pseudobulbar palsy, which may have permanent consequences. Therefore, it is generally recommended to aim for a correction rate of 0.5 to 1.0 mmol/L per hour in these patients[16].

Treating the underlying small cell lung cancer is crucial to control the production of ADH and resolve SIADH. Fluid intake may be limited, typically to less than 1000 mL per day, depending on the severity of hyponatremia and the amount of urine being excreted. It is advisable to discontinue any medications that may be contributing to the condition, such as opiates, certain antidepressants, vinca alkaloids, and cisplatin, if feasible [17].

The main pharmacological treatments for SIADH include demeclocycline (300-600 mg orally twice daily) and vasopressin receptor antagonists (Conivaptan, 20-40 mg/d IV Tolvaptan 10-60 mg/d orally). Demeclocycline works by interfering with the renal response to ADH and does not require concurrent fluid restriction to achieve its desired effect. The response to demeclocycline can take anywhere from a few days to several weeks. Possible adverse effects of demeclocycline include nausea, loss of appetite, diarrhoea, and renal toxicity, particularly in individuals with pre-existing kidney impairment. Prolonged use of demeclocycline can potentially result in the development of diabetes insipidus [18] (excretion of overly dilute urine leading to hypernatremia).

Acromegaly

The most common tumors that secrete ectopic GHRH or GH are bronchial carcinoids and pancreatic islet cell tumors but have also been reported to be associated with small cell lung carcinoma[19,20].

The routine assessment of circulating GHRH (growth hormone-releasing hormone) in individuals with acromegaly can aid in the early identification of GHRH overproduction, as plasma levels above 0.3 ng/mL are highly indicative of a GHRH-secreting tumor. On the other hand, ectopic acromegaly, characterized by abnormal GH secretion, exhibits elevated basal GH levels that are not suppressed by glucose load, along with low or undetectable plasma GHRH levels.

For the management of ectopic acromegaly, complete surgical removal of the tumor is the most effective treatment option, typically resulting in the normalization of GH levels and regression of acromegalic features. In cases where residual, recurrent, or inoperable lesions are present, octreotide and other somatostatin analogues have been successfully used as treatment alternatives.

NEUROLOGIC SYNDROMES

Paraneoplastic cerebellar degeneration

Paraneoplastic cerebellar degeneration is an inflammatory autoimmune process that occurs due to the destruction of cerebellar Purkinje cells by onconeural antibodies; these antibodies are produced by the immune system in response to a protein that is expressed by tumor cells. Clinical features include dizziness, oscillopsia, double vision, nausea, vomiting, dysarthria, gait and limb ataxia, and variable dysphagia. Downbeat nystagmus can be found.

Diagnosis is FDG-PET: increased metabolism (early stage) then decreased (late stage). MRI may show cerebellar atrophy in late-stage and the presence of onconeuronal antibodies associated with malignancy some of which are shown in Table 2.

These usually do not improve with treatment. However case reports of improvement after tumor removal, plasma exchange, IVIG (400-1000 mg/day to a total of 2-3 g), immunosuppressants (prednisolone at 1 mg/kg, cyclophosphamide and rituximab) [1,21].

Antibody	Associated malignancy
Anti-Yo antibodies	Ovary, breast
Anti-Ri	Breast, gynecological, SCLC
Anti-VGCC ab	SCLC
Anti-Tr	Hodgkin's lymphoma/no tumor
Anti-mGluR1 ab	Hodgkin's lymphoma/no tumor

Table 2- onconeuronal antibody associated with PCD.

Opsoclonus-myoclonus ataxia

Opsoclonus-myoclonus (OM), also known as opsoclonus-myoclonus-ataxia (OMA), is a distinct type of movement disorder. It is characterized by involuntary, rapid eye movements that occur in multiple directions (opsoclonus), along with muscle jerks (myoclonus) that can affect various parts of the body, including the face, head/neck, trunk, and limbs[22]. It is associated with malignancy in 20% of cases, most commonly SCLC [23]. Antineural antibodies detected in lung cancer include anti-Ri, anti-Hu, anti-amphiphysin and P/Q-type VGCC antibodies.

Clinical features include opsoclonus-myoclonus, hypotonia, ataxia, behavioural changes, irritability if untreated progress to encephalopathy, coma, and death.

Unlike many other paraneoplastic neurological syndromes (PNS), paraneoplastic opsoclonus-myoclonus (OM) can show improvement in symptoms either on its own, after treating the underlying tumor, or with the use of medications such as clonazepam or thiamine [21]. Response to immunotherapy is also seen (glucocorticoid, ACTH, plasma exchange, IVIG, rituximab, cyclophosphamide).

Autonomic neuropathy

Paraneoplastic autonomic neuropathy is a type of neuropathy that is associated with small-cell lung cancer (SCLC). It occurs as a result of an immune-mediated response to the presence of the tumor. The autonomic nerves, which control involuntary functions such as heart rate, blood pressure, digestion,

and sweating, are affected, leading to dysregulation of these processes. Symptoms can vary and may include orthostatic hypotension (low blood pressure upon standing), gastrointestinal dysfunction, abnormal sweating, urinary bladder dysfunction, and sexual dysfunction [24].
It is associated with anti-Hu, anti-CRMP5, anti-nAchR and anti-amphiphysin. Treatment of the underlying tumor, such as chemotherapy, radiation therapy, or surgery, is crucial to control cancer and potentially improve neuropathic symptoms along with symptomatic treatment [25].

Stiff person syndrome

It is characterized by progressive muscle rigidity (lower limb > upper limb), stiffness, and painful spasm triggered by auditory, sensory or emotional stimuli. Symptoms improve with sleep and general anaesthesia. Diagnosis made by EPS: showing continuous motor unit activity along with antibodies: Anti GAD, Anti amphiphysin ab, Glycine R ab.
Treatment consists of treating the underlying tumor. Glucocorticoids, Drugs that increase GABA-ergic transmission can also be used (diazepam, baclofen, sodium valproate, tiagabine, vigabatrin) [26].

Retinal blindness

Retinal blindness associated with small cell lung cancer (SCLC) refers to a rare but serious paraneoplastic syndrome known as cancer-associated retinopathy (CAR). It is characterized by visual disturbances and vision loss due to an immune-mediated response against retinal antigens expressed by the tumor [27].
The treatment of retinal blindness associated with SCLC primarily focuses on managing underlying cancer and providing supportive care for visual symptoms. This may involve interventions such as low-vision aids, adaptive devices, and vision rehabilitation programs to optimize remaining vision and improve daily functioning [28].

Lambert Eaton syndrome

LEMS (Lambert Eaton myasthenic syndrome) is commonly associated with small-cell lung cancer, it is a neuromuscular disorder that primarily affects the presynaptic function of neuromuscular transmission. It is characterized by a reduction in the release of acetylcholine at the neuromuscular junction. This impaired release leads to symptoms such as weakness in the proximal muscles, diminished reflexes, and post-tetanic potentiation. LEMS can also cause autonomic changes such as dry mouth, sluggish light reflex, and erectile dysfunction. More rapid progression in paraneoplastic LEMS than non-paraneoplastic [29].
Diagnosis is made by nerve conduction studies, which show low motor amplitude, normal sensory amplitude, post-exercise facilitation of CMAP, Repetitive nerve stimulation and exercise testing shows an increase in CMAP with RNS (post-activation facilitation) and post-exercise facilitation. It is associated with antibodies against P/Q-type VGCC (50% association with malignancy) [30].
The treatment approach for LEMS involves three main aspects: addressing underlying cancer, providing symptomatic relief, and utilizing immunotherapy. Upon the identification of cancer, appropriate treatment for the cancer should be initiated. It is noteworthy that a significant proportion of LEMS patients with small cell lung cancer (SCLC) have a localized form of the disease, and successful treatment of cancer can result in long-lasting clinical improvement [21] .
As a symptomatic treatment, the first-line approach for LEMS is the use of 3,4-aminopyridine. This medication acts by blocking VGKC (voltage-gated potassium channels) and prolonging the opening time of VGCC (voltage-gated calcium channels) and action potentials at the motor nerve terminals. Consequently, there is an increase in calcium influx into the nerve terminal, leading to the release of acetylcholine (Ach). Recent research has indicated that aminopyridines can specifically target the VGCC β subunit, enhancing synaptic and neuromuscular transmission. This treatment

aims to alleviate the symptoms associated with LEMS [30].

Immunotherapy is another important component of LEMS treatment. It involves the use of immunomodulatory agents to modify the immune response and reduce the autoimmune attack on the neuromuscular junction. Specific immunotherapeutic approaches may include the use of corticosteroids, intravenous immunoglobulins (IVIG), plasmapheresis, or immunosuppressive medications. The choice of immunotherapy depends on various factors, including the individual patient's condition and response to treatment [21].

Limbic encephalitis

LE is typically suspected based on clinical presentation characterized by a rapid or gradual onset of symptoms over a period of a few days to several months. These symptoms may include changes in personality, irritability, depression, seizures, memory impairment, confusion, and other related manifestations.

Paraneoplastic limbic encephalitis is often associated with an underlying malignancy, such as small-cell lung cancer, ovarian cancer, or testicular cancer [21,30].

Electroencephalographic (EEG) findings in patients with limbic encephalitis often show slow activity in specific areas of the brain or generalized slow activity. Additionally, epileptic activity in the temporal lobes may be observed. Magnetic resonance imaging (MRI) studies commonly reveal high signal intensities in the temporal lobes, either unilaterally or bilaterally, in approximately 70% to 80% of patients. This can be visualized using T2-weighted or fluid-attenuated inversion recovery (FLAIR) imaging techniques. Cerebrospinal fluid (CSF) analysis is another important diagnostic tool, as it may demonstrate evidence of inflammation in around 80% of limbic encephalitis cases. This can include findings such as increased white blood cell count (pleocytosis), elevated protein levels, elevated IgG levels, and the presence of oligoclonal bands. CSF analysis is valuable for supporting the clinical diagnosis of limbic encephalitis and ruling out other conditions like carcinomatous meningitis [31].

Early recognition and treatment of the underlying tumor, along with immunotherapy or other immunosuppressive treatments, are crucial for managing Paraneoplastic LE and improving neurological outcomes [21,30].

Subacute sensory neuropathy

Subacute sensory neuropathy (SSN) can be diagnosed when the following criteria are met: a gradual onset within 12 weeks, a Rankin score indicating moderate disability (severity of at least 3), the initial presentation of numbness with accompanying pain and sensory disturbances, involvement of both arms and legs (resembling a "gloves and stockings" distribution), often with asymmetry at the onset. Electrophysiological tests reveal significant impairment of sensory fibres and the absence of sensory nerve action potentials in at least one sensory nerve field [21,32]. Motor nerves may show minimal impairment, while tendon reflexes are typically depressed or absent. Patients may also exhibit autonomic, cerebellar, or cerebral abnormalities. SSN is present in approximately 75% of patients with paraneoplastic encephalomyelitis, with a predominant occurrence in 50% and a clinically pure form in 25% [33,34].

In patients with SCLC, SSN is typically associated with the presence of anti-Hu antibodies. Less commonly, SSN in SCLC patients can be linked to anti-CV2 (CRMP-5), anti-amphiphysin, or anti-Yo antibodies. There have been reported cases of SSN associated with SCLC in which patients tested positive for ganglionic neuronal acetylcholine receptor (nAChR) antibodies [35]. Early and complete treatment of underlying SCLC is the key to treatment.

CONCLUSION

Paraneoplastic syndromes are often linked to lung cancer, especially small-cell lung cancer. The objective of this review was to provide a concise overview of the present understanding and approaches to managing paraneoplastic syndromes associated with small-cell lung cancer. Recent advancements have enhanced our comprehension of these syndromes and provided improved options for diagnosis and treatment. Recognizing paraneoplastic syndromes in small cell lung cancer can result in earlier detection and diagnosis, potentially enhancing the overall prognosis and survival rates for patients, it also opens a gateway for greater research for more targeted therapy.

Declaration by Authors
Ethical Approval: Not Required
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

Glossary

ADH- Antidiuretic Hormone
AVP- Arginine Vasopressin
CRH- Corticotropin-Releasing Hormone
ECS- Ectopic Cushing's Syndrome
EEG- Electroencephalogram
GHRH- Growth Hormone-Releasing Hormone
LE- Limbic Encephalitis
LEMS - Lambert-Eaton Myasthenic Syndrome
MRI- Magnetic Resonance Imaging
OM- Opsoclonus-Myoclonus
OMA- Opsoclonus-Myoclonus-Ataxia
PTHrP- Parathormone Related Peptide
RNS- Repetitive Nerve Stimulation
SCLC- Small Cell Lung Cancer
SIADH- Syndrome of Inappropriate Antidiuretic Hormone Secretion
SSN- Subacute Sensory Neuropathy
VGKC - Voltage-Gated Potassium Channels

REFERENCES

1. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010; 85:838–54.
2. Picard Leblanc G, Blais N, Tehfe M, Routy B, Florescu M. Prognostic impact of paraneoplastic syndromes in patients with small cell lung cancer, real-world data. JCO. 2019;37: e20082–e20082.
3. Koh ET, Seow A, Ong B, Ratnagopal P, Tjia H, Chng HH. Adult-onset polymyositis/dermatomyositis: clinical and laboratory features and treatment response in 75 patients. Ann Rheum Dis. 1993; 52:857–61.
4. Thiers BH, Sahn RE, Callen JP. Cutaneous manifestations of internal malignancy. CA Cancer J Clin. 2009; 59:73–98.
5. Waller R, Ahmad N. 1. TIF1-γ associated dermatomyositis. Rheumatology Advances in Practice. 2019;3: rkz030.
6. Barbosa SL-S, Rodien P, Leboulleux S, Niccoli-Sire P, Kraimps J-L, Caron P, et al. Ectopic adrenocorticotropic hormone-syndrome in medullary carcinoma of the thyroid: a retrospective analysis and review of the literature. Thyroid. 2005; 15:618–23.
7. Morandi U, Casali C, Rossi G. Bronchial typical carcinoid tumors. Semin Thorac Cardiovasc Surg. 2006; 18:191–8.
8. Teves DA. Clinical Approach of Cushing Syndrome Resulting From ACTH-Producing Metastatic Neuroendocrine Tumor: The Endocrinologist. 2005; 15:401–4.
9. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. The Lancet Diabetes & Endocrinology. 2021; 9:847–75.
10. Nieman LK. Medical therapy of Cushing's disease. Pituitary. 2002; 5:77–82.
11. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005; 352:373–9.
12. Renaghan AD, Rosner MH. Hypercalcemia: etiology and management. Nephrology Dialysis Transplantation. 2018; 33:549–51.
13. Lumachi F, Brunello A, Roma A, Basso U. Medical treatment of malignancy-associated hypercalcemia. Curr Med Chem. 2008; 15:415–21.
14. Hansen O, Sørensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis. Lung Cancer. 2010; 68:111–4.

15. Gross AJ, Steinberg SM, Reilly JG, Bliss DP, Brennan J, Le PT, et al. Atrial natriuretic factor and arginine vasopressin production in tumor cell lines from patients with lung cancer and their relationship to serum sodium. Cancer Res. 1993; 53:67–74.
16. Adrogué HJ, Tucker BM, Madias NE. Diagnosis and Management of Hyponatremia: A Review. JAMA. 2022; 328:280–91.
17. Raftopoulos H. Diagnosis and management of hyponatremia in cancer patients. Support Care Cancer. 2007; 15:1341–7.
18. Rondon H, Badireddy M. Hyponatremia. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470386/
19. Faglia G, Arosio M, Bazzoni N. Ectopic acromegaly. Endocrinol Metab Clin North Am. 1992; 21:575–95.
20. Biswal S, Srinivasan B, Dutta P, Ranjan P, Vaiphei K, Singh RS, et al. Acromegaly caused by ectopic growth hormone: a rare manifestation of a bronchial carcinoid. Ann Thorac Surg. 2008; 85:330–2.
21. de Beukelaar JW, Sillevis Smitt PA. Managing paraneoplastic neurological disorders. Oncologist. 2006; 11:292–305.
22. Ohara S, Iijima N, Hayashida K, Oide T, Katai S. Autopsy case of opsoclonus-myoclonus-ataxia and cerebellar cognitive affective syndrome associated with small cell carcinoma of the lung. Mov Disord. 2007; 22:1320–4.
23. Digre KB. Opsoclonus in adults. Report of three cases and review of the literature. Arch Neurol. 1986; 43:1165–75.
24. Benarroch EE. The clinical approach to autonomic failure in neurological disorders. Nat Rev Neurol. 2014; 10:396–407.
25. Koike H, Sobue G. Paraneoplastic neuropathy. Handb Clin Neurol. 2013; 115:713–26.
26. de Albóniga-Chindurza A, Riva E, Jiménez-Huete A, Graus F, Franch O. Paraneoplastic stiff person syndrome with small cell carcinoma of the bladder and anti-Ri antibodies. Clinical Neurology and Neurosurgery. 2018; 173:194–5.
27. Ohguro H, Ogawa K, Maeda T, Maeda A, Maruyama I. Cancer-associated retinopathy induced by both anti-recoverin and anti-hsc70 antibodies in vivo. Invest Ophthalmol Vis Sci. 1999; 40:3160–7.
28. Weleber RG, Watzke RC, Shults WT, Trzupek KM, Heckenlively JR, Egan RA, et al. Clinical and electrophysiologic characterization of paraneoplastic and autoimmune retinopathies associated with antienolase antibodies. Am J Ophthalmol. 2005; 139:780–94.
29. Kesner VG, Oh SJ, Dimachkie MM, Barohn RJ. Lambert-Eaton Myasthenic Syndrome. Neurol Clin. 2018; 36:379–94.
30. Didelot A, Honnorat J. Update on paraneoplastic neurological syndromes. Curr Opin Oncol. 2009; 21:566–72.
31. Altabakhi IW, Babiker HM. Paraneoplastic Limbic Encephalitis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK519523/
32. Blaes F, Jauss M, Kraus J, Oschmann P, Krasenbrink I, Kaps M, et al. Adult paraneoplastic opsoclonus-myoclonus syndrome associated with antimitochondrial autoantibodies. J Neurol Neurosurg Psychiatry. 2003; 74:1595–6.
33. Graus F, Keime-Guibert F, Reñe R, Benyahia B, Ribalta T, Ascaso C, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain. 2001; 124:1138–48.
34. Sillevis Smitt P, Grefkens J, de Leeuw B, van den Bent M, van Putten W, Hooijkaas H, et al. Survival and outcome in 73 anti-Hu positive patients with paraneoplastic encephalomyelitis/sensory neuronopathy. J Neurol. 2002; 249:745–53.
35. Antoine J-C, Camdessanché J-P. Peripheral nervous system involvement in patients with cancer. Lancet Neurol. 2007; 6:75–86.

How to cite this article: Archana Rajan, Abhisek Sahoo. Paraneoplastic syndromes in small cell lung cancer: a narrative review. *International Journal of Research and Review*. 2023; 10(7): 660-670.
DOI: *https://doi.org/10.52403/ijrr.20230778*

******