Endocrine paraneoplastic syndromes in lung cancer: A call for clinical vigilance (Review)

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Abstract. Endocrine paraneoplastic syndromes (PNS) are uncommon but clinically impactful manifestations associated with malignancies, particularly lung cancer, most notably small-cell lung cancer. These syndromes arise from ectopic hormone production by malignant cells, causing systemic effects that are independent of direct tumor invasion or metastasis. Their presentation often precedes or signals recurrence of the primary cancer, underscoring the importance of early recognition and targeted intervention. Common endocrine PNS in lung cancer include syndrome of inappropriate antidiuretic hormone secretion, hypercalcemia, Cushing syndrome, carcinoid syndrome, and other hormonal imbalances such as non-islet cell tumor hypoglycemia, gynecomastia and acromegaly. The pathophysiology of these conditions involves ectopic secretion of bioactive substances such as hormones and cytokines, leading to diverse clinical manifestations. Accurate diagnosis necessitates a combination of biochemical assessments, imaging modalities, and histopathological evaluations to differentiate paraneoplastic processes from primary endocrine disorders. Management strategies emphasize treating the underlying malignancy, often through chemotherapy, radiotherapy, or surgical intervention, alongside symptomatic therapies tailored to the specific endocrine abnormality. Multidisciplinary care is critical for optimizing outcomes and enhancing patients' quality of life. The current review highlights the need for heightened clinical vigilance and a systematic approach to diagnosing and managing endocrine PNS in lung cancer. By fostering early detection and comprehensive management, clinicians can significantly improve prognostic outcomes for affected individuals.

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Contents

1. Introduction

Lung cancer remains a significant global health concern, affecting ~2.5 million individuals annually and exhibiting the highest mortality rates among all cancer types, accounting for ~18.7% of cancer-related deaths (1,2). The elevated mortality rate is primarily attributed to the disease's tendency to present with atypical or asymptomatic manifestations, as well as the limited participation of high-risk individuals in systematic preventative screening programs. Consequently, lung cancer is often diagnosed at advanced stages (3). In some cases, systemic signs and symptoms unrelated to the primary tumor may arise as paraneoplastic manifestations.

Paraneoplastic syndrome (PNS) encompasses a heterogeneous group of disorders caused by either the secretion of functional amines, peptides, hormones, or cytokines by the

tumor or an aberrant immune cross-reactivity between the tumor and normal tissues (4). PNS has been estimated to affect ~8% of all patients with cancer (5). Among malignancies, lung cancer [particularly small-cell lung cancer (SCLC)] is strongly associated with PNS. Notably, the presence and severity of PNS do not correlate with the size of the primary tumor. In some cases, PNS may manifest before the primary cancer is diagnosed, while in others, it may appear later in the disease course or serve as an early indication of cancer recurrence (6).

The present review aims to provide a comprehensive overview of endocrine PNS in lung cancer, with a particular focus on its pathophysiology, clinical presentation, diagnosis and management. By highlighting the importance of early recognition and timely intervention, the current review seeks to equip healthcare professionals with practical insights to optimize patient care.

2. Pathophysiology of endocrine PNS

Endocrine PNS represents a distinct subset of paraneoplastic disorders in which neoplastic cells produce bioactive substances such as hormones, peptides and cytokines, leading to endocrine dysfunction independent of direct tumor invasion or metastasis. These endocrine abnormalities can often precede the diagnosis of cancer and are not necessarily associated with the primary organ or tissue of origin. While the pathogenesis of endocrine PNS is well-characterized in endocrine tumors, its mechanisms in non-endocrine malignancies remain less clearly defined. In these cases, the neoplasm may either mimic endogenous hormone activity or interfere with normal endocrine regulatory pathways, contributing to complex and often misleading clinical presentations (7).

3. Diagnostic criteria

Clinicians should maintain a high index of suspicion for endocrine PNS in both oncologic and non-oncologic patients when there is evidence of dysregulated hormone production. Key indicators include abnormally elevated hormone levels, a significant concentration gradient between the hormone levels in the venous effluent from the tumor and the arterial circulation, the presence of bioactive and/or immunoreactive hormone in tumor extracts, and the identification of relevant hormone mRNA within tumor tissue. Furthermore, tumor cells may exhibit the ability to synthesize and secrete the hormone *in vitro*.

Additional clinical clues reinforcing the tumor's role in hormone production include the presence of endocrine or metabolic disturbances in a patient with a known malignancy, remission of these abnormalities following successful treatment (for example, surgery, radiotherapy, or chemotherapy), and the recurrence of endocrine dysfunction in parallel with tumor relapse (8).

4. Syndrome of inappropriate antidiuretic hormone (SIADH)

The first suspicion of inappropriate antidiuretic hormone (ADH) secretion was raised by Schwartz in 1957 when he observed euvolemic, hypotonic hyponatremia in two patients with bronchogenic lung cancer, despite normal renal and adrenal function (9). This hypothesis was confirmed several years later, around 1963, when a molecule exhibiting ADH-like activity was isolated from cancer biopsy material (10).

ADH is synthesized in the neurohypophysis and plays a crucial role in fluid homeostasis by binding to renal receptors to reduce free water excretion. Under normal physiological conditions, when plasma osmolality exceeds 280 mOsm/kg, the pituitary gland increases ADH secretion to enhance renal water reabsorption, maintaining fluid and osmotic balance. In patients with SCLC, ectopic ADH production leads to impaired free-water excretion in the distal renal tubules, resulting in hyponatremia. SCLC cells have been found to express ADH mRNA and actively synthesize and release ADH, leading to elevated plasma ADH levels. However, some patients with SCLC-associated hyponatremia exhibit no detectable plasma ADH. In such cases, the tumor may express mRNA for atrial natriuretic peptide (ANP), which is subsequently secreted, leading to elevated plasma ANP concentrations and an alternative mechanism contributing to hyponatremia (11,12).

The diagnosis of SIADH is based on specific laboratory findings, including decreased plasma osmolality (<275 mOsm/kg), inappropriately concentrated urine (>100 mOsm/kg), euvolemic status, elevated urine sodium (>20 mEq/l), and normal thyroid and cortisol function, with no history of diuretic use (13). SIADH is commonly associated with disorders affecting the central nervous system and the lungs. Although it is most frequently linked to SCLC, it has also been reported in malignancies of the brain, prostate, bladder, pancreas, adrenal glands and digestive tract, as well as in mesothelioma, thymoma, sarcoma and hematologic malignancies (14).

Management of SIADH in cases of severe symptomatic hyponatremia requires immediate intervention with hypertonic saline. Administration of 100 ml of 3% NaCl, up to three doses, is recommended to achieve an initial increase in plasma sodium (pNa) of 4 to 6 mmol/l, alleviating symptoms and reducing intracranial pressure. In chronic SIADH, pNa correction should be gradual to avoid osmotic demyelination syndrome, with an increase of 4 to 8 mmol/l per day, not exceeding 10 mmol/l per day. The primary treatment for chronic SIADH is fluid restriction to <1,000 ml/day, though this approach is effective in only ~50% of patients. Second-line therapies include tolvaptan, urea, sodium-glucose cotransporter 2 inhibitors, or high-dose salt tablets. The cornerstone of SIADH management remains the treatment of the underlying malignancy, either through oncological or surgical interventions (15).

5. Hypercalcemia

Hypercalcemia of malignancy (HCM) is a common metabolic complication in patients with cancer, frequently observed in hospitalized individuals. Its prevalence varies widely, ranging from 2-30%, with an estimated annual incidence of 1-2%. This variability is largely dependent on the type of malignancy and the disease stage (16,17). HCM is predominantly associated with solid tumors, with lung cancer (particularly squamous cell carcinoma) being a common culprit. The two primary mechanisms underlying hypercalcemia in patients with cancer

are humoral hypercalcemia of malignancy (HCM) and bone metastases.

HCM, a PNS, arises when tumors secrete parathyroid hormone (PTH)-related peptide (PTHrP), leading to increased calcium levels. Though rare, lung cancer can also ectopically produce PTH. Additionally, 1,25-dihydroxyvitamin D secretion is frequently observed in hematologic malignancies. Granulocyte colony-stimulating factor has also been implicated in HHM by promoting osteoclast activation over time, further exacerbating hypercalcemia (18).

Hypercalcemia disrupts normal cellular function and manifests with a broad spectrum of symptoms. Neuromuscular effects include confusion, fatigue and muscle weakness. Gastrointestinal symptoms such as nausea, abdominal pain and constipation are common. Renal complications may involve increased thirst and urination, kidney stone formation and dehydration. Cardiovascular manifestations include hypertension and a shortened QT interval on ECG. Bone-related symptoms, including bone pain, osteoporosis and osteitis fibrosa cystica, are also prevalent. The mnemonic 'Stones, bones, abdominal moans and psychic groans' serves as a useful reminder of the diverse clinical manifestations of hypercalcemia (19).

Management of hypercalcemia begins with fluid resuscitation using 0.9% NaCl, which reduces serum calcium levels by expanding intravascular volume and enhancing renal calcium excretion. Diuretics such as furosemide may be used following volume expansion to further promote calcium elimination. Corticosteroids such as prednisolone are particularly effective for hypercalcemia associated with lymphoid malignancies but have limited efficacy in solid tumors and may interfere with diagnostic assessments. Bisphosphonates, which inhibit bone resorption, are highly effective in managing hypercalcemia caused by multiple myeloma and solid tumors with skeletal metastases, though they have limited utility in HHM due to their minimal effect on PTHrP-mediated hypercalcemia. Calcitonin provides rapid, short-term relief by inhibiting bone resorption and increasing renal calcium excretion, but its utility is limited by the rapid onset of tachyphylaxis, necessitating frequent dosing (20).

Cinacalcet, a calcium-mimetic agent, effectively lowers calcium levels by increasing the sensitivity of the calcium-sensing receptor, making it particularly useful in cases of humoral hypercalcemia that are resistant to conventional treatments (21). The mechanisms of PTHrP-induced hypercalcemia in lung cancer are demonstrated in Fig. 1.

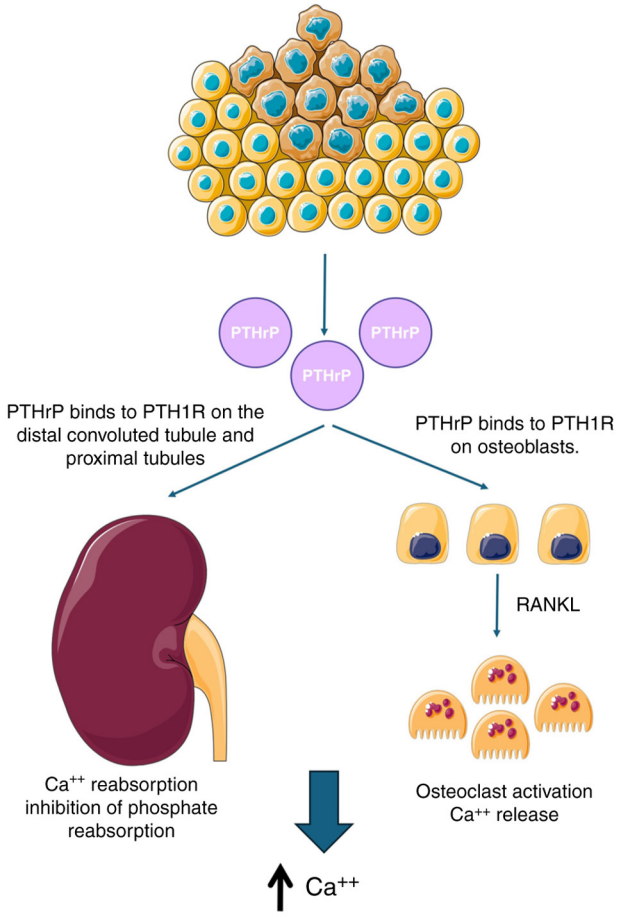

Figure 1. Mechanisms of PTHrP-induced hypercalcemia in lung cancer. Parts of this image are derived from the free medical site http://smart.servier.com/ (accessed on 15 December 2024) by Servier, licenced under a Creative Commons Attribution 4.0 Unported Licence. PTHrP, parathyroid hormone-related protein.

6. Cushing syndrome

Cushing syndrome is a well-recognized paraneoplastic phenomenon associated primarily with SCLC and bronchial carcinoid tumors. In total, ~5-10% of all Cushing syndrome (hypercortisolism) cases are of paraneoplastic origin, with neuroendocrine lung tumors accounting for ~50-60% of these cases. This condition arises due to the ectopic production of adrenocorticotropic hormone (ACTH) by tumor cells, leading to excessive cortisol production by the adrenal glands. This phenomenon, known as ectopic Cushing syndrome, results in a broad range of clinical manifestations. Unlike SIADH and hypercalcemia, symptoms of paraneoplastic Cushing syndrome frequently precede the diagnosis of cancer. Additionally, recurrence of hypercortisolism may serve as an indicator of tumor relapse.

The clinical presentation of ectopic Cushing syndrome includes weight gain, hypertension, diabetes mellitus, muscle weakness and characteristic skin changes such as easy bruising and purple striae. Patients often exhibit classic Cushingoid features, including moon facies, truncal obesity and wide violaceous striae (22).

In lung cancer, ectopic ACTH production is most commonly observed in SCLC, which accounts for ~10-15% of all lung cancer cases. SCLC is a highly aggressive malignancy that is frequently diagnosed at an advanced, metastatic stage. Paraneoplastic ACTH secretion by SCLC results in bilateral adrenal hyperplasia and excessive cortisol production. The biochemical profile of ectopic Cushing syndrome typically includes elevated plasma ACTH and cortisol levels, with a disruption of the normal diurnal rhythm of cortisol secretion. Specific laboratory findings associated with this condition include a serum cortisol level >29 μg/dl, a urinary free cortisol level >47 μg/24 h, and a midnight ACTH level >100 ng/l (23).

The management of Cushing syndrome in patients with lung cancer is complex and requires a multidisciplinary approach. The first-line treatment involves targeting the underlying malignancy with chemotherapy, which can reduce tumor

burden and consequently lower ectopic hormone production. Medical therapies such as ketoconazole, metyrapone, or mifepristone can be used to control hypercortisolism by inhibiting adrenal steroidogenesis. Additionally, somatostatin analogs (for example, octreotide) have shown efficacy in reducing hormone secretion and controlling symptoms. In refractory cases, bilateral adrenalectomy may be considered to alleviate severe hypercortisolism; however, this is a last-resort option due to significant surgical risks and the complexities of postoperative adrenal insufficiency management (4,24).

7. Carcinoid syndrome

Carcinoid syndrome is a rare but significant paraneoplastic phenomenon that can occur in patients with lung cancer, particularly those with bronchial carcinoid tumors. Bronchial carcinoids are a type of neuroendocrine tumor (NET) that originates from neuroendocrine cells in the lung. These tumors can secrete various bioactive amines and peptides, most notably serotonin, which is responsible for the clinical manifestations of carcinoid syndrome (25).

The classic symptoms of carcinoid syndrome include flushing, diarrhea, bronchoconstriction, and, in advanced cases, carcinoid heart disease characterized by fibrosis of the heart valves. Flushing is typically episodic, affecting the face and upper chest, and can be triggered by stress, alcohol, or specific foods. Diarrhea can be severe and debilitating, leading to significant weight loss and electrolyte imbalances. Bronchoconstriction presents as wheezing and asthma-like symptoms, often resulting in misdiagnosis as a primary pulmonary disorder (26). In lung cancer, bronchial carcinoids are less common than their gastrointestinal counterparts but remain crucial to recognize due to their distinct clinical behavior and therapeutic implications. These tumors are classified as typical or atypical carcinoids based on histological criteria, with atypical carcinoids exhibiting a more aggressive clinical course and a higher likelihood of metastasis (25).

The diagnosis of carcinoid syndrome involves detecting elevated levels of serotonin metabolites, such as 5-hydroxy-indole-acetic acid in urine, and serum chromogranin A, a key marker for NETs. Imaging studies, including computed tomography (CT) and somatostatin receptor scintigraphy (SRS), can help localize the primary tumor and assess disease extent. Somatostatin receptor imaging can identify nearly 80% of primary tumors and is particularly useful for detecting metastatic disease (27).

The treatment of carcinoid syndrome in lung cancer requires a combination of surgical, medical and supportive approaches. Somatostatin analogs, such as octreotide and lanreotide, are the first-line treatment for controlling symptoms. These medications inhibit the release of serotonin and other vasoactive substances, thereby managing flushing, diarrhea and wheezing. While they are effective in symptom control, they may not completely prevent long-term complications (27). In cases of metastatic disease, additional therapies may be required, including peptide receptor radionuclide therapy (PRRT), systemic chemotherapy, or targeted therapies. Advances in genomic research have led to the exploration of targeted therapies, particularly inhibitors of the mammalian target of rapamycin (mTOR) pathway, such as everolimus, which have shown promise in treating progressive NETs and controlling hormone secretion (28). Surgical resection of the primary tumor remains the cornerstone of treatment and can be curative in localized disease. Removing the tumor significantly reduces or eliminates hormone secretion, leading to symptom resolution. In metastatic cases, debulking surgery may still provide symptomatic relief (29). The mechanisms of carcinoid syndrome in lung cancer are illustrated in Fig. 2.

8. Non-islet cell tumor hypoglycemia (NITCH)

Hypoglycemia can be life-threatening and requires accurate diagnosis. Cancer-related hypoglycemia arises through three mechanisms: Insulin-secreting tumors (for example, insulinomas), tumor-induced organ damage impairing glucose regulation, and NITCH, where tumors secrete substances such as 'big' IGF-II, which mimic insulin (30). Insulin-like growth factor (IGF)-2-mediated hypoglycemia, though rare (1 case/million person-years), has significant morbidity and mortality, yet literature on its course and treatment remains limited (31).

'Big'-IGF-II, an abnormal IGF-2 variant (10-20 kDa), forms a binary complex with IGFBP-3, enabling easier vascular passage and enhanced glucose-lowering effects (32). It is commonly associated with fibrous tumors, liver-originating tumors, hemangiopericytomas and mesotheliomas (33). Although reported in lung cancer cases, no strong correlation exists with specific subtypes (30,34,35).

Diagnosing hypoglycemia in non-diabetic patients requires evaluating medication effects, severe illness, organ dysfunction and hormone deficiencies while also differentiating endogenous hyperinsulinism. If a tumor is suspected, NITCH should be considered. Diagnostic measures include serum glucose, insulin, proinsulin, C-peptide, β-hydroxybutyrate and hypoglycemic drug screening. If NITCH is suspected, additional IGF-I, IGF-II and growth hormone (GH) assessments should be performed (36).

Endocrine Society guidelines suggest NITCH presents with glucose <55 mg/dl, insulin ≤3 U/ml, proinsulin ≤5 pmol/l, C-peptide ≤0.2 nmol/l and β-hydroxybutyrate ≤2.7 mmol/l, with no hypoglycemic agents detected. Unlike transient hypoglycemia, GH remains low due to negative feedback. While IGF-II levels may be normal (275-750 ng/ml), IGF-I is often below 100 ng/ml, leading to an elevated IGF-II/IGF-I ratio, occasionally exceeding 10:1-a valuable NITCH marker (32).

Currently, no commercial test exists for big IGF-II, necessitating specialized research labs (37). If the hypoglycemia etiology is unclear, a glucagon stimulation test may help: A rise in glucose indicates a hormonal origin, whereas an inadequate response suggests insufficient liver glycogen reserves (38). Cross-sectional imaging of the chest, abdomen, and pelvis is crucial for tumor identification (32).

Immediate management of hypoglycemia involves oral or intravenous glucose administration. While complete tumor resection is the definitive treatment, reports of recurrence following disease-relapse exist (32). Glucagon injections provide short-term relief, while continuous glucagon infusions may be effective in selective cases (39). Diazoxide and octreotide have shown limited efficacy (40,41). Glucocorticoids remain the most extensively studied treatment, effectively reducing IGF-II levels and controlling hypoglycemia in

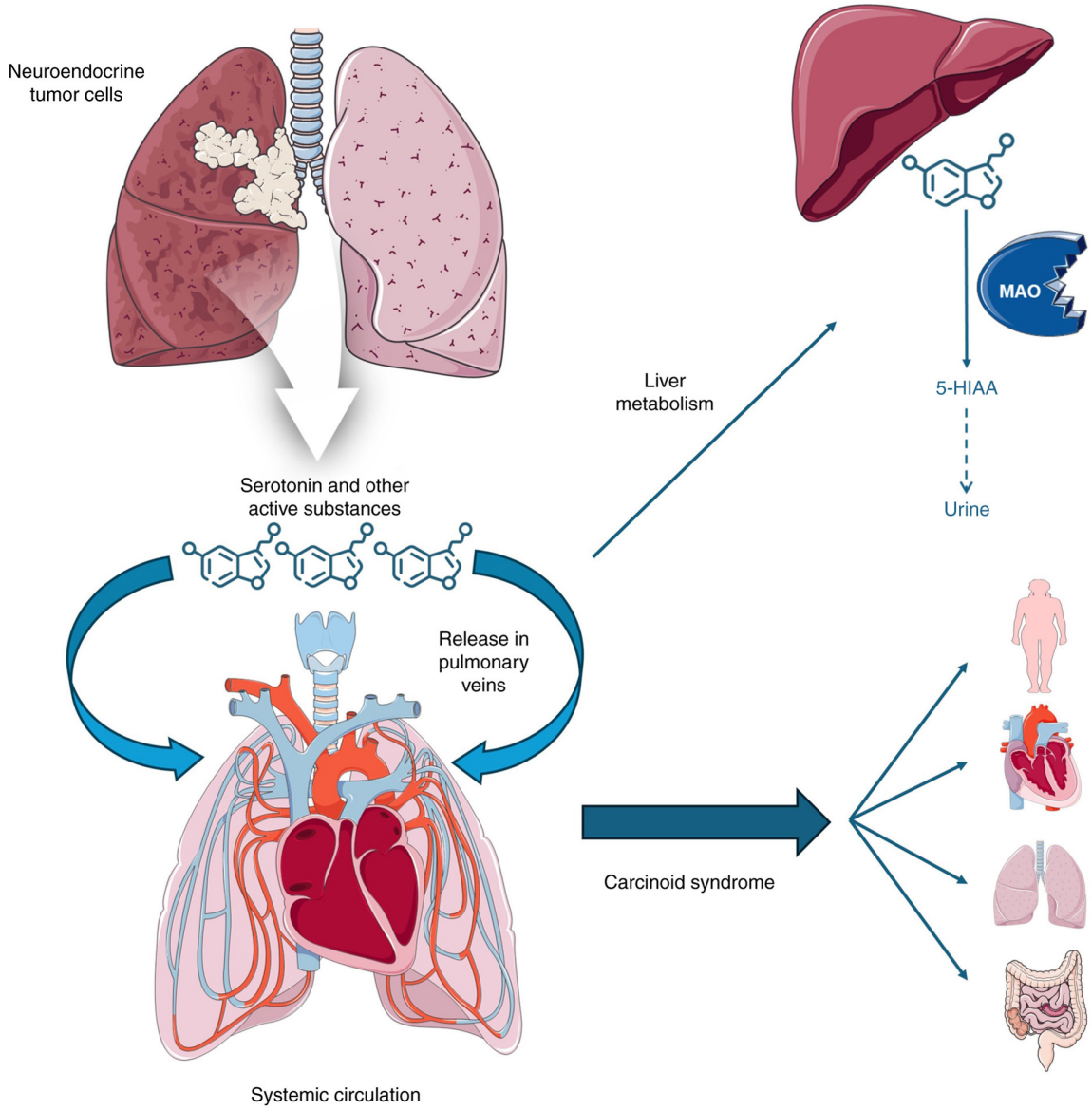

Figure 2. Mechanisms of carcinoid syndrome in lung cancer. Parts of this image are derived from the free medical site http://smart.servier.com/ (accessed on 15 December 2024) by Servier, licenced under a Creative Commons Attribution 4.0 Unported Licence. 5-HIAA, 5-hydroxy-indole-acetic acid.

25-30% of cases. Combination therapy with recombinant human GH may enhance outcomes, though the absence of randomized controlled trials limits definitive treatment guidelines (42,43).

9. Acromegaly

In 1959, Altman and Schutz described a case of acromegaly in a patient who did not improve following pituitary irradiation but showed significant clinical improvement after the surgical removal of a lung carcinoid tumor. This case provided early evidence that ectopic production of growth-hormone-releasing hormone (GHRH) by a non-pituitary tumor can lead to acromegaly and emphasized the importance of considering ectopic hormone secretion when patients fail to respond to standard pituitary-directed treatments (44). Although rare, autonomous hormone secretion due to GHRH or, in exceptional cases, direct secretion of GH occurs in <1% of acromegaly cases, with bronchial carcinoid tumors being the most frequently implicated ectopic source (45).

The diagnosis of acromegaly begins with clinical suspicion and measurement of serum IGF-1, which is typically elevated. To confirm the diagnosis, an Oral Glucose Tolerance Test is performed, as glucose administration normally suppresses GH levels, whereas in acromegaly, GH remains elevated. Imaging with magnetic resonance imaging (MRI) of the pituitary gland is then conducted to identify a pituitary tumor responsible for excess GH production. Additional endocrine testing may include evaluating other pituitary hormones and ruling out alternative conditions with similar clinical manifestations. A definitive diagnosis is established by integrating clinical symptoms, biochemical findings and imaging results, which confirm persistently elevated IGF-1, inadequate GH suppression following glucose intake, and the presence of a pituitary tumor.

Table I. Overview of endocrine paraneoplastic syndromes in lung cancer.

Syndrome	Primary hormone/ chemical involved	Pathophysiology	Clinical presentation	Diagnosis	Management
Syndrome of inappropriate ADH	ADH	Ectopic production of ADH leading to impaired water excretion and hyponatremia	Hyponatremia, headache, nausea, confusion, seizures	Low plasma osmolality, concentrated urine, euvolemia, and elevated urine sodium	Fluid restriction, hypertonic saline, tolvaptan, and addressing underlying malignancy
Cushing syndrome	ACTH	Ectopic ACTH production causing excess cortisol secretion and hypercortisolism	Weight gain, hypertension, diabetes, muscle weakness, moon face	Elevated ACTH and cortisol, loss of cortisol diurnal rhythm	Chemotherapy, metyrapone, ketoconazole, octreotide, or bilateral adrenalectomy
Hypercalcemia	PTHrP	Secretion of PTHrP or osteolytic activity of bone metastases, leading to increased calcium levels	Bone pain, confusion, muscle weakness, constipation	Elevated serum calcium, suppressed PTH, and increased PTHrP levels	Hydration, bisphosphonates, calcitonin, cinacalcet, and addressing malignancy
Carcinoid syndrome	Serotonin	Secretion of serotonin and other bioactive substances by neuroendocrine tumors	Flushing, diarrhea, broncho-spasm, heart valve fibrosis	Elevated urinary 5-hydroxy-indole-acetic acid, elevated plasma chromogranin A, somatostatin receptor scintigraphy	Octreotide, lanreotide, peptide receptor radionuclide therapy, surgical resection
Non-islet cell Tumor Hypoglycemia (NITCH)	IGF-II	Ectopic production of 'big' IGF-II mimicking insulin and lowering glucose levels	Hypoglycemia, confusion, sweating, weakness	Low glucose, low insulin, low C-peptide, elevated IGF-II/IGF-I ratio	Glucocorticoids, surgery, glucagon infusion, addressing underlying tumor
Acromegaly	GHRH	Ectopic GHRH production leading to excess growth hormone and IGF-1	Enlarged hands/feet, coarse facial features, headache	Elevated IGF-1, lack of GH suppression after glucose load, pituitary magnetic resonance imaging	Surgery, somatostatin analogs, GH receptor antagonists, addressing ectopic source
Zollinger-Ellison syndrome	Gastrin	Ectopic production of gastrin causing hyper-secretion of gastric acid	Recurrent peptic ulcers, GERD, diarrhea, abdominal pain	Elevated fasting gastrin, secretin stimulation test	Proton pump inhibitors, somatostatin analogs, surgery, chemotherapy for underlying malignancy
Gynecomastia	β-HCG	Ectopic β-HCG secretion leading to an imbalance in testosterone and estrogen	Breast enlargement, tenderness	Elevated β-HCG, imaging to rule out testicular and other tumors	Treat underlying malignancy, consider hormonal therapy

Table I. Continued.

Syndrome	Primary hormone/ chemical involved	Pathophysiology	Clinical presentation	Diagnosis	Management
Hyperprolactinemia	Prolactin	Ectopic production of prolactin leading to suppression of the hypothalamic-pituitary-gonadal axis	Galactorrhea, amenorrhea, infertility, decreased libido	Elevated prolactin, imaging to exclude pituitary source	Dopamine agonists (cabergoline, bromocriptine), surgery for non-responsive cases

ADH, antidiuretic hormone; ACTH, adrenocorticotropic hormone; PTHrP, parathyroid hormone-related peptide; IGF-II, insulin-like growth factor II; GHRH, growth hormone releasing hormone; β-HCG, β-human chorionic gonadotropin.

A patient with biochemically confirmed acromegaly but a normal pituitary MRI presents a diagnostic and therapeutic challenge, as the tumor may be too small to be detected. In such cases, further evaluation is necessary to investigate the possibility of ectopic hormone secretion. Additional tests should include serum GHRH measurement and imaging techniques such as SRS (octreoscan), which has a reported sensitivity of 97%, as well as thoracic and abdominal imaging to identify potential ectopic sources of hormone production (46,47).

The preferred treatment approach for ectopic acromegaly is surgical resection of the tumor, as it offers the highest chance of cure and symptom resolution. Whenever possible, complete surgical removal of the ectopic source should be pursued to achieve optimal clinical outcomes (48).

10. Zollinger-Ellison syndrome

Zollinger-Ellison syndrome is a rare paraneoplastic disorder caused by the ectopic secretion of gastrin, typically by gastrin-producing NETs known as gastrinomas. While the majority of gastrinomas are located in the abdomen, particularly in the pancreas and duodenum, ectopic gastrin production has been reported in association with lung cancer, primarily in NETs such as atypical carcinoids and SCLC (49).

The hallmark of Zollinger-Ellison syndrome is hypergastrinemia, which leads to excessive gastric acid secretion and severe peptic ulcer disease. Patients commonly present with abdominal pain, chronic diarrhea, gastroesophageal reflux disease and weight loss. The excessive acid production results in multiple and recurrent peptic ulcers that are often resistant to standard medical therapy. Chronic diarrhea in Zollinger-Ellison syndrome is typically caused by the direct effects of excess gastric acid on the intestinal mucosa, leading to malabsorption (50).

In the setting of lung cancer, diagnosing ectopic gastrin production can be challenging due to the overlap of symptoms with other gastrointestinal and PNSs. The diagnosis is based on clinical presentation, biochemical testing and imaging studies. A high degree of suspicion is warranted in patients with recurrent, severe peptic ulcers that fail to respond to conventional treatment. Biochemical confirmation involves measuring elevated fasting serum gastrin levels, which indicate the presence of gastrin-secreting tumors. The secretin stimulation test is often used to confirm the diagnosis; an abnormal rise in gastrin levels following secretin administration strongly suggests Zollinger-Ellison syndrome. Imaging studies such as CT, MRI and SRS help localize the gastrin-producing tumors, which are most commonly found in the pancreas or duodenum. Endoscopic ultrasound and biopsy can further aid in precise localization and tissue diagnosis. Accurate identification of the condition is essential for effective management, which typically includes both pharmacologic control of gastric acid secretion and surgical intervention (51,52).

The treatment of Zollinger-Ellison syndrome associated with lung cancer requires a comprehensive approach that targets both the excessive gastric acid secretion and the underlying malignancy. Management usually begins with high-dose proton pump inhibitors, such as omeprazole or esomeprazole, to control the severe acid hypersecretion, often at doses higher than those used for standard peptic ulcer disease (53,54). In

cases where the gastrinoma is localized, surgical resection is considered; however, if the tumors are metastatic or inoperable, somatostatin analogs such as octreotide or lanreotide can help reduce gastrin secretion (55). For patients with metastatic disease or those who are not surgical candidates, somatostatin analogs remain an essential therapeutic option (56,57).

Managing Zollinger-Ellison syndrome in the context of lung cancer is particularly complex and requires a multidisciplinary approach involving oncologists, gastroenterologists and surgeons. Treatments directed at the lung cancer, including chemotherapy, radiation therapy, or targeted therapies, may influence the progression of gastrin-secreting tumors, especially if they are part of a broader NET syndrome. Emerging therapies such as everolimus, which targets tumors with mTOR pathway activation, as well as immunotherapy and PRRT, are being explored as potential treatment strategies for metastatic disease (58-60).

11. Gynecomastia

Gynecomastia, the enlargement of male breast tissue due to hormonal imbalance, can occur as a PNS in various cancers, affecting ~2.4% of patients with lung cancer (61,62). The therapeutic approach to gynecomastia depends on identifying the underlying cause. The initial evaluation should exclude common pathological factors, including medication use, chronic liver or kidney disease, or androgen therapy in men with hypogonadism (63). If no apparent cause is found, pathological gynecomastia should be considered.

The first step in hormonal assessment involves measuring levels of luteinizing hormone, testosterone, dehydroepiandrosterone sulfate, thyroid function, estradiol, and the beta subunit of human chorionic gonadotropin (β-hCG) (63). When β-hCG levels are elevated, further investigation is warranted to identify potential testicular tumors, which are the most common cause, as well as extragonadal germ cell tumors or hCG-secreting trophoblastic tumors. Although rare, non-trophoblastic tumors, including those of the lung, kidney, liver and stomach, can also cause gynecomastia via ectopic hCG production. Among these, lung cancer is the most frequently implicated (64-66).

Only a few cases of gynecomastia associated with lung cancer have been documented in the literature, predominantly in non-small cell lung cancer, particularly adenocarcinoma, and typically presenting as bilateral gynecomastia (67). The underlying mechanism often involves ectopic β-hCG production by tumor cells, which has been confirmed using immunohistochemical methods (7,68).

The treatment of gynecomastia in the context of lung cancer is directly tied to managing the underlying malignancy, typically through chemotherapy and/or surgical resection, depending on the type and stage of the tumor (61,69).

12. Hyperprolactinemia

Ectopic production of prolactin associated with SCLC remains a rare manifestation, with only a few cases documented in the literature to date (70-72). The clinical presentation of hyperprolactinemia results from suppression of the hypothalamic-pituitary-gonadal axis and varies depending on the patient's sex and age.

In women, hyperprolactinemia may present with oligomenorrhea, amenorrhea, galactorrhea, decreased libido, infertility, and, in prolonged cases, possible osteopenia. Chronic hyperprolactinemia can also lead to hyperandrogenism, causing hirsutism and acne, potentially due to increased secretion of adrenal dehydroepiandrosterone sulfate and reduced levels of sex hormone-binding globulin, resulting in elevated free testosterone levels.

In men, hyperprolactinemia can manifest as erectile dysfunction, decreased libido, infertility, gynecomastia, reduced bone mass, and, in rare cases, galactorrhea. Over time, men may also experience fatigue, reduced muscle mass and an increased risk of osteopenia (73).

Persistent hyperprolactinemia, after excluding common causes such as non-fasting blood samples, excessive exercise, recent medication use, chest wall trauma or surgery, renal disease, cirrhosis, or recent seizures, may indicate a paraneoplastic etiology. In such cases, further imaging evaluation is warranted to investigate underlying neoplasms (74).

The treatment of hyperprolactinemia includes dopamine receptor agonists, such as cabergoline or bromocriptine, which effectively suppress prolactin secretion. In cases where medical therapy fails, surgical removal of the tumor may be necessary (75).

Emerging research suggests that aberrant prolactin activation could serve as a biomarker for lung cancer aggressiveness, with elevated prolactin levels correlating with rapid disease progression. Additionally, histone deacetylase inhibitors have been proposed as a potential therapeutic strategy, highlighting the role of prolactin in both diagnosis and treatment (71). The endocrine PNSs in lung cancer are summarized in Table I.

13. Conclusions

Endocrine PNSs in lung cancer are rare but clinically significant, often serving as early indicators of malignancy or disease recurrence. The present review highlights the pathophysiology, diagnostic challenges and management strategies of these syndromes, emphasizing the importance of early recognition and a multidisciplinary approach. Given their impact on patient outcomes, heightened clinical vigilance and systematic evaluation are essentisal to improving early diagnosis and optimizing treatment.

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Authors' contributions

MEK and VEG conceptualized the study. MEK, VEG, DAS, DA, MPY and MS made a substantial contribution to data interpretation and analysis and wrote and prepared the draft of the manuscript. MEK and VEG analyzed the data and provided critical revisions. All authors contributed to

manuscript revision, read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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