

Paraneoplastic syndromes

Systemic manifestations of pulmonary neoplasms

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Learning objectives

- Define paraneoplastic syndromes and separate them from local tumor effects or metastasis.
- Link characteristic ectopic products and immune responses to their clinical syndromes.
- Recognize subtype tendencies: Small cell carcinoma versus squamous cell carcinoma.
- Explain why a systemic syndrome may precede discovery of a pulmonary tumor.

What makes a syndrome paraneoplastic?

- Symptoms are not explained by the physical location of the primary or metastatic tumor.
- They are not simply the expected function of the normal tissue of tumor origin.
- They arise from ectopic mediators or cancer-associated systemic host responses.
- The syndrome may be the first clinically detectable sign of an occult cancer.

Three pathways to systemic symptoms

Local tumor or invasion

- Airway obstruction, collapse or infection
- Superior vena cava compression
- Neural invasion in a Pancoast tumor

Paraneoplastic pathway

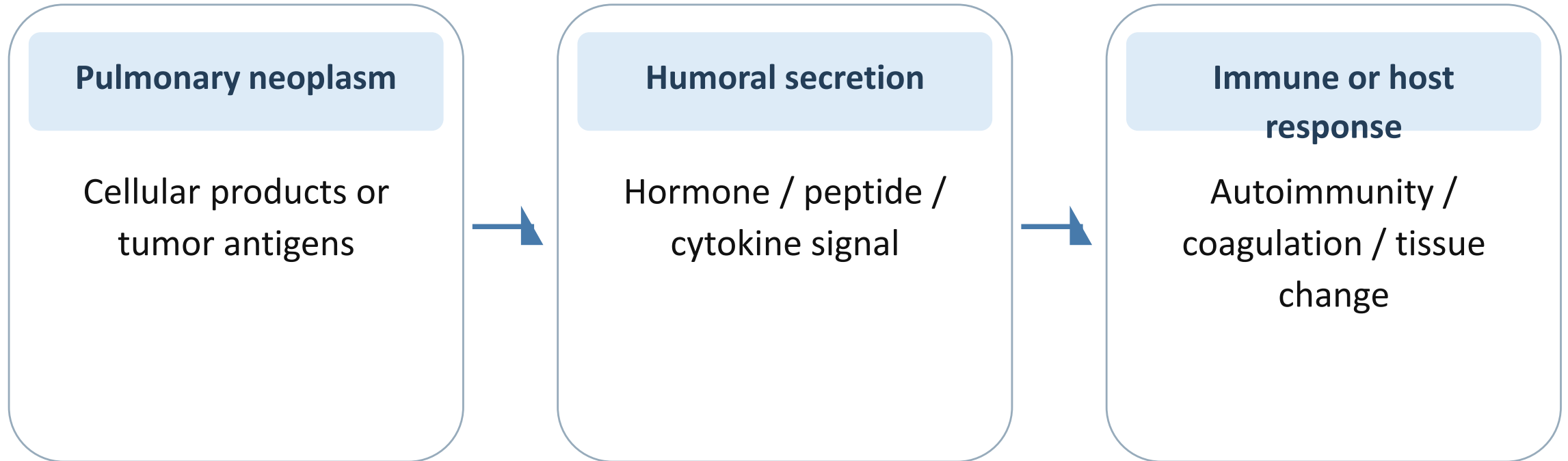
- Ectopic ACTH, ADH or PTH-related protein
- Autoimmune neuromuscular dysfunction
- Clotting or connective-tissue changes

Anatomic invasion $\neq$ distant paraneoplastic effect.

Why recognition matters

- Systemic findings can appear before a lung lesion is clinically apparent.
- Endocrine, neurologic, and vascular complications may be clinically significant or lethal.
- Some findings imitate metastatic spread and can distort staging assumptions.
- An unexplained compatible syndrome should prompt evaluation for an underlying malignancy.

Two broad mechanistic routes



Schematic

Different syndromes have distinct causal mechanisms; The routes are not interchangeable.

Lung cancer: Relevant histologic context

- The major carcinomas are adenocarcinoma, squamous cell carcinoma, and small cell carcinoma.
- Small cell carcinoma shows neuroendocrine differentiation and can secrete ectopic peptides.
- Squamous cell carcinoma is a classic setting for PTH-related protein–associated hypercalcemia.
- Any histologic subtype can occasionally produce any one of the described hormones.

Histology predicts tendencies—not certainty

Tumor category	Typical association	Important qualifier
Small cell carcinoma	ACTH and ADH secretion	Predominant, not exclusive
Squamous cell carcinoma	Hypercalcemia	Often linked to PTH-related protein
Other lung carcinomas	Variable paraneoplastic findings	No subtype absolutely excluded

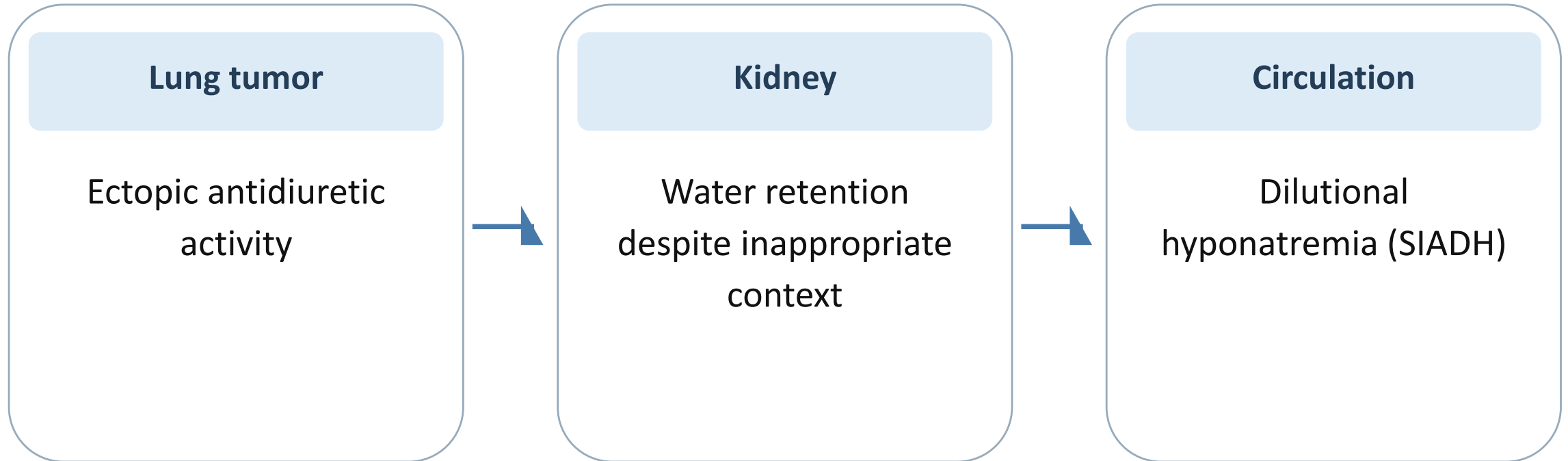
How frequent are endocrine paraneoplastic effects?

- Clinically significant syndromes related to the listed humoral mediators occur in approximately 1%–10% of lung cancer patients.
- This range describes the specified endocrine or hormone-like factors in the lung chapter.
- It should not be confused with the broader estimate of all paraneoplastic syndromes across cancers.
- An uncommon syndrome may nevertheless be the dominant presenting problem.

The endocrine repertoire of lung tumors

Tumor-derived mediator	Recognized manifestation
Antidiuretic hormone (ADH)	Syndrome of inappropriate ADH secretion
Adrenocorticotrophic hormone (ACTH)	Cushing syndrome
PTH-related protein and other factors	Hypercalcemia
Calcitonin / gonadotropins	Hypocalcemia / gynecomastia
Serotonin and bradykinin	Carcinoid syndrome

ADH-mediated paraneoplastic hyponatremia



Schematic

SIADH: The causal distinction

- The tumor-associated problem is inappropriate antidiuretic activity—not compression of the kidney.
- Retained water lowers the concentration of sodium in extracellular fluid.
- This is a systemic endocrine effect even when the thoracic lesion is small.
- Robbins especially associates ectopic ADH production with small cell carcinoma.

Case: Unexplained hyponatremia

Vignette

An individual is found to have persistent hyponatremia. Further evaluation reveals a pulmonary mass that proves to be small cell carcinoma.

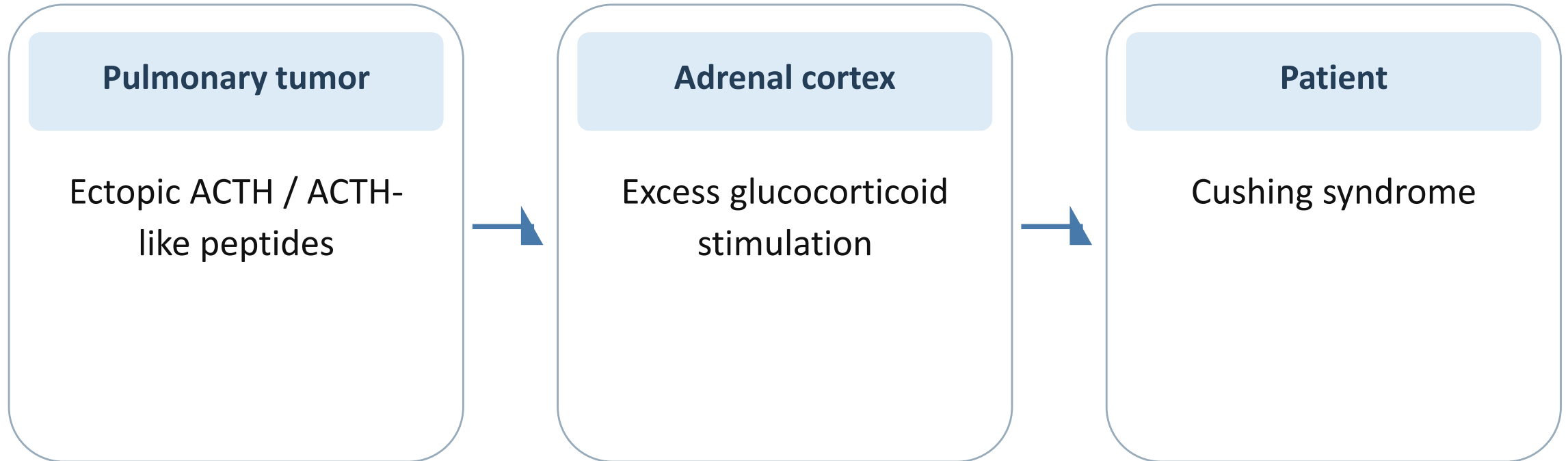
Interpretation

- Recognize a systemic endocrine effect.
- Identify the likely ectopic mediator.

Answer

The textbook association is ectopic ADH secretion causing SIADH; Direct tumor spread is not needed.

ACTH-mediated ectopic Cushing syndrome

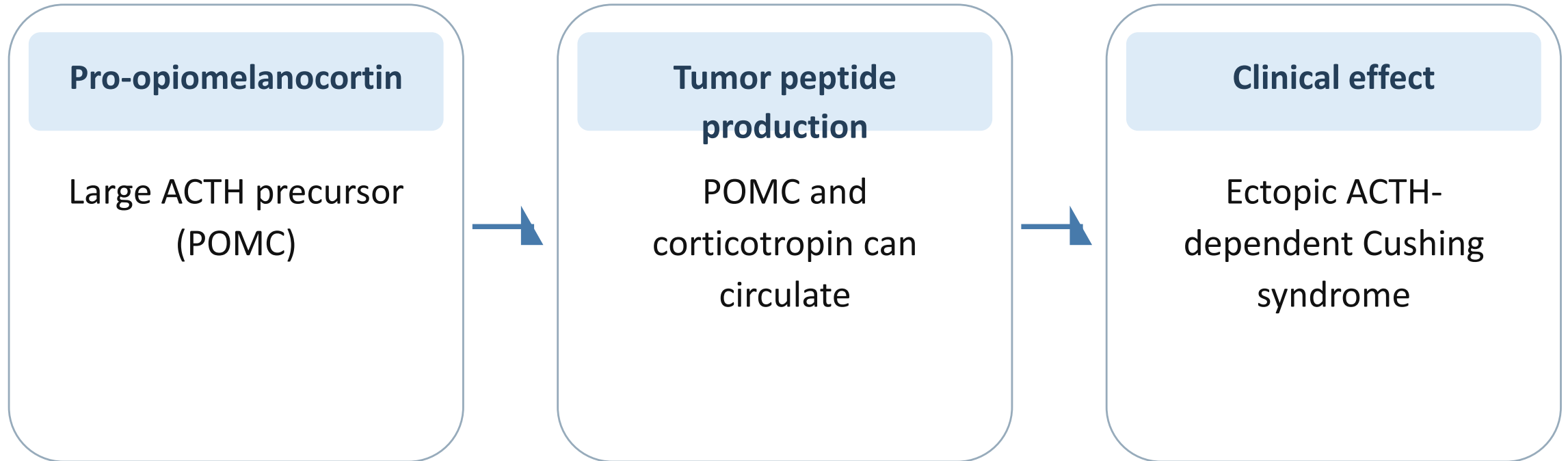


Schematic

Why small cell carcinoma is prominent

- Ectopic ACTH production is predominantly associated with small cell carcinoma among lung cancers.
- The tumor can release ACTH or ACTH-like products without an endocrine tissue of origin.
- Clinical hypercortisolism can therefore signal an underlying lung malignancy.
- The relationship is characteristic but not absolute.

POMC processing and ectopic corticotropin



Schematic

Ectopic versus pituitary ACTH secretion

Ectopic ACTH in lung cancer

- Produced outside native pituitary tissue
- POMC and corticotropin may both be elevated
- Paraneoplastic interpretation

Pituitary ACTH excess

- ACTH from pituitary cells
- Source notes circulating POMC distinction
- Not a paraneoplastic syndrome

POMC as a distinguishing biologic observation, not a standalone clinical test algorithm.

Case: Cushing syndrome before a lung diagnosis

Vignette

A patient develops Cushing syndrome; Imaging subsequently identifies a small cell pulmonary carcinoma.

Interpretation

- Ectopic secretion explains the endocrine phenotype.
- The syndrome may precede recognition of the pulmonary lesion.

Answer

ACTH or an ACTH-like peptide is the textbook-supported mechanism.

Hypercalcemia: Two distinct cancer mechanisms

- Bone destruction can release calcium when tumors involve the skeleton.
- Extraosseous tumors can also produce circulating calcemic substances.
- Only the second mechanism is paraneoplastic humoral hypercalcemia.
- Distinguishing mechanisms prevents incorrect attribution of hypercalcemia to osseous metastasis.

Humoral hypercalcemia versus osteolysis

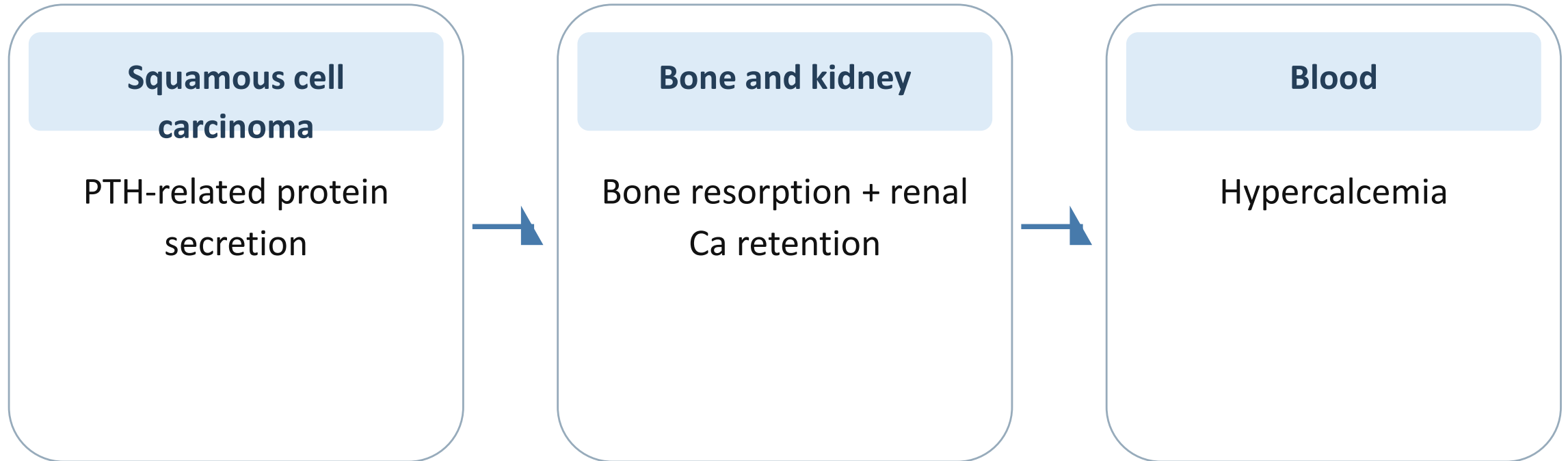
Humoral paraneoplastic

- Extraosseous tumor releases calcemic factor
- PTH-related protein is a leading mediator
- Does not require skeletal metastases

Osteolytic cancer-associated

- Primary bone tumor or bone metastasis causes resorption
- Calcium liberated locally from bone
- Not classified as paraneoplastic here

PTH-related protein raises serum calcium



Schematic

PTH-related protein and PTH: Shared receptor

- PTH-related protein has partial structural homology with parathyroid hormone.
- Both interact with the PTH/PTH-related protein G-protein–coupled receptor.
- PTH-related protein promotes skeletal calcium mobilization and renal calcium conservation.
- It also diminishes renal phosphate transport, contributing to its biochemical phenotype.

Why squamous carcinoma is a classic association

- The most common lung tumor linked to hypercalcemia is squamous cell carcinoma.
- Its associated humoral mechanism is commonly PTH-related protein secretion.
- PTH-related protein is also produced in small amounts by normal epithelial tissues.
- Association with squamous differentiation does not make the finding histologically diagnostic.

Other mediators in malignancy-associated hypercalcemia

Mediator in Robbins	Mechanistic grouping
PTH-related protein	Humoral calcemic factor
Interleukin-1 and tumor necrosis factor	Inflammatory cytokines
Transforming growth factor- α	Growth-factor pathway
Prostaglandin E and vitamin D metabolites	Other implicated humoral pathways

Not every mediator has the same evidentiary strength in every tumor.

Interpreting hypercalcemia in a lung cancer patient

- First consider whether skeletal lesions could explain an osteolytic mechanism.
- If a humoral effect is implicated, PTH-related protein is the textbook's principal candidate.
- Tumor histology shifts suspicion toward squamous carcinoma but is not definitive.
- A systemic metabolic abnormality alone cannot establish tumor subtype or disease stage.

Case: Hypercalcemia without bone metastases

Vignette

A lung squamous cell carcinoma is accompanied by hypercalcemia; No osseous metastatic explanation is evident.

Interpretation

- Select the paraneoplastic humoral pathway.
- Explain the biologic consequence for bone and renal handling.

Answer

PTH-related protein acting on the PTH/PTHrP receptor is the leading mechanism.

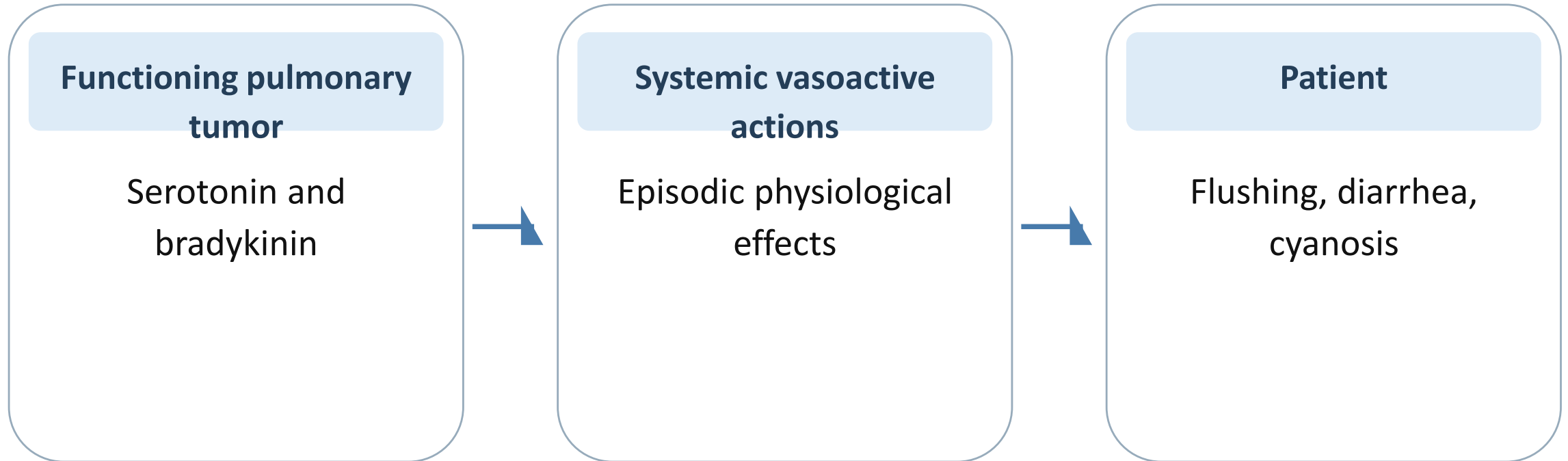
Calcitonin: A less familiar endocrine association

- Calcitonin is listed among hormone-like substances elaborated by lung cancers.
- The lung chapter links tumor-associated calcitonin production with hypocalcemia.
- This is distinct from the common hypercalcemia pathway of PTH-related protein.
- The source does not provide a frequency or subtype-specific rule for this effect.

Ectopic gonadotropins and gynecomastia

- Gonadotropin production is included among paraneoplastic activities of lung tumors.
- The recognized endocrine manifestation is gynecomastia.
- The mechanism differs from ADH-related sodium changes and PTH-related calcium changes.
- Its presence does not identify a unique lung carcinoma histotype.

Vasoactive mediators and carcinoid syndrome



Schematic

Pulmonary carcinoid syndrome

- Functioning bronchial carcinoid tumors may produce vasoactive amines.
- Intermittent diarrhea, flushing, and cyanosis.
- Approximately 10% of bronchial carcinoids develop the classic syndrome.
- Most pulmonary carcinoids do not show this secretory activity.

Pulmonary carcinoid and small cell carcinoma

Carcinoid tumor

- Neuroendocrine lung neoplasm with often indolent behavior
- Secretion may lead to carcinoid syndrome
- Typical and atypical forms

Small cell carcinoma

- High-grade, aggressive neuroendocrine carcinoma
- Ectopic ADH and ACTH especially associated
- Usually widely disseminated when recognized

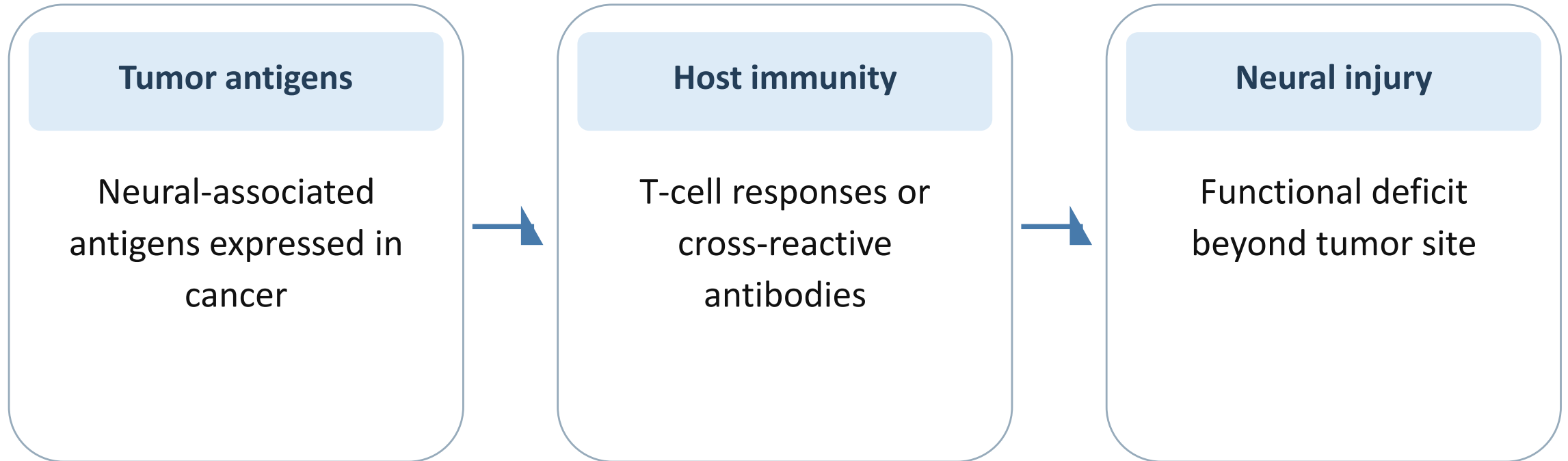
Endocrine synthesis by mediator

Syndrome	Mediator	Lung association
SIADH	ADH	Small cell predominant
Cushing syndrome	ACTH	Small cell predominant
Hypercalcemia	PTH-related protein	Squamous predominant
Carcinoid syndrome	Serotonin / bradykinin	Functional bronchial carcinoid

Immune-mediated neurologic syndromes

- Systemic neuromuscular manifestations may occur without neural invasion.
- Examples include Lambert–Eaton myasthenic syndrome and sensory neuropathy.
- The broader paraneoplastic spectrum includes encephalitis and cerebellar degeneration.
- The mechanisms frequently involve immunologic cross-reaction against host neural structures.

A model for onconeural autoimmunity



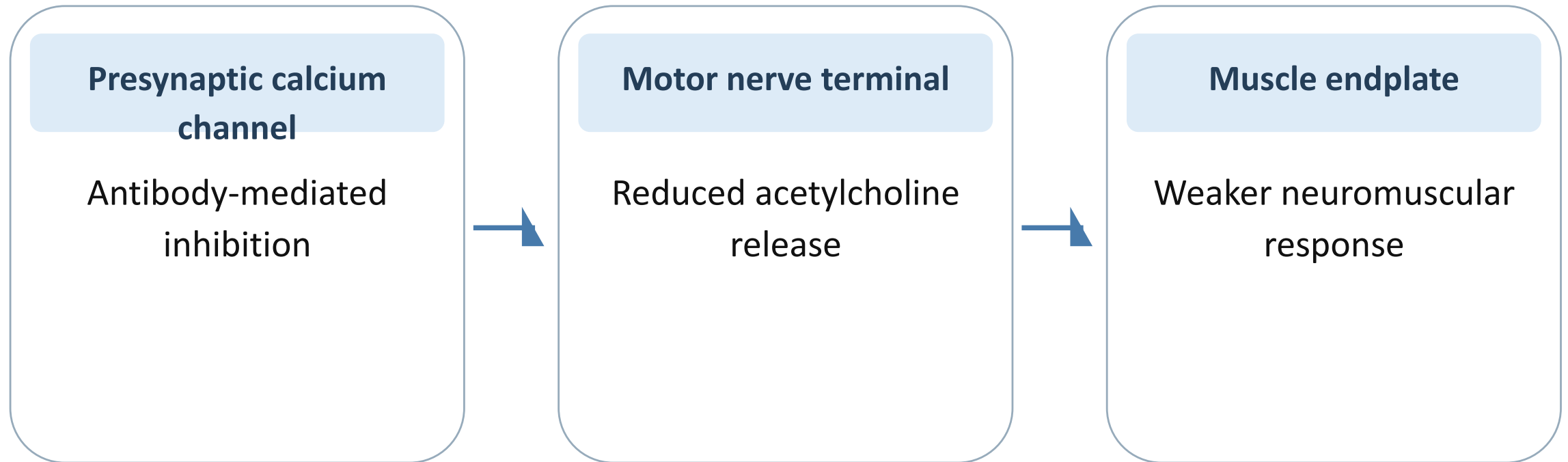
Schematic

This as a proposed mechanism; Not all syndromes are fully understood.

Lambert–Eaton: The target is presynaptic

- Antibodies inhibit a presynaptic calcium channel at the neuromuscular junction.
- Reduced calcium-dependent acetylcholine release impairs transmission.
- The clinical result is weakness, particularly involving the extremities.
- This is an antibody-associated paraneoplastic mechanism—not direct muscle metastasis.

Neuromuscular transmission in Lambert–Eaton



Schematic

Facilitation with repeated activity

- Lambert–Eaton differs from classical myasthenia gravis in its response to repetitive activity.
- A brief interval of muscle use can augment strength.
- Rapid repetitive stimulation increases the muscle response.
- These features support a presynaptic transmission defect.

Lambert–Eaton versus myasthenia gravis

Lambert–Eaton

- Presynaptic calcium-channel antibodies
- Extremity weakness typical
- Response increases after brief activity

Myasthenia gravis

- Postsynaptic ACh receptor / related targets
- Ocular symptoms frequently prominent
- Weakness typically worsens with exertion

Why a neuromuscular syndrome may precede cancer

- Approximately half of Lambert–Eaton patients have an underlying malignancy.
- The associated cancer is most often small cell carcinoma of the lung.
- Neurologic symptoms sometimes appear years before cancer detection.
- The textbook proposes tumor expression of the relevant calcium channel as an autoimmune trigger.

Case: Weakness improves after muscle use

Vignette

A patient has limb weakness that transiently improves after brief repetitive contractions; A pulmonary neoplasm is subsequently found.

Interpretation

- Identify the neuromuscular-junction level.
- Name the expected autoantibody target.

Answer

Lambert–Eaton: A presynaptic calcium channel, with small cell carcinoma as an important cancer association.

Sensory neuropathy as a paraneoplastic clue

- Lung carcinoma may be accompanied by a peripheral neuropathy.
- The lung chapter emphasizes a predominantly sensory presentation.
- The broader neoplasia chapter considers immune-mediated nerve injury among possible mechanisms.
- Clinical localization is distinct from tumor compression of a nerve.

Central neurologic paraneoplastic patterns

- The broader textbook discussion lists encephalitis and cortical cerebellar degeneration.
- These syndromes may reflect an aberrant anti-tumor response cross-reacting with neural antigens.
- T-cell injury is implicated; Neuronal cross-reactive antibodies are found in some cases.
- The text emphasizes incomplete understanding of their causes.

Neural invasion versus paraneoplastic neurologic disease

Direct tumor effect

- Apical tumor invades local sympathetic structures
- Pancoast-associated Horner syndrome
- Anatomic localization is explanatory

Remote immune effect

- Lambert–Eaton or sensory neuropathy
- No direct neural invasion required
- Immune-mediated dysfunction is implicated

Cutaneous paraneoplastic patterns

- Acanthosis nigricans is among the dermatologic changes associated with lung cancer.
- The neoplasia chapter also describes cancer-associated dermatomyositis.
- Skin findings can appear before recognition of the primary neoplasm.
- Neither skin disorder is specific to lung cancer.

Acanthosis nigricans: Recognizable morphology

- Gray-black, thickened patches of skin with a velvety surface are characteristic.
- Stomach, lung and uterine carcinomas among associated cancers.
- The proposed pathways include immune signals and epidermal growth-factor activity.
- Abrupt onset in an appropriate clinical context can prompt malignancy assessment.

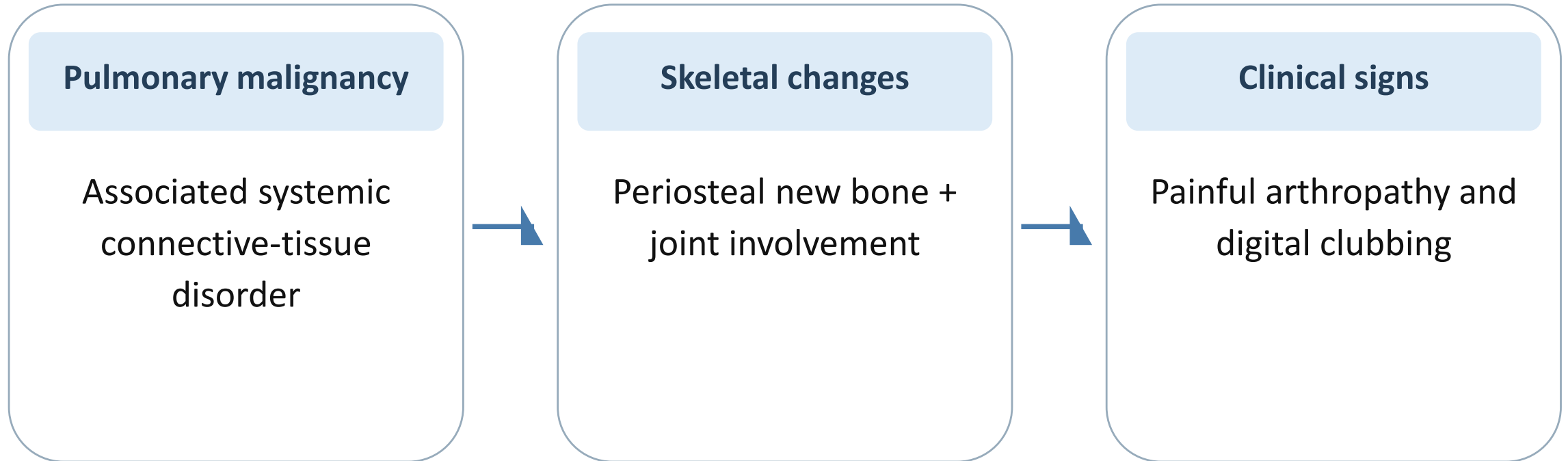
Dermatomyositis in the paraneoplastic spectrum

- The generalized paraneoplastic classification includes dermatomyositis.
- Bronchogenic and breast carcinomas are listed associations.
- The proposed mechanism is immunologic rather than local skin invasion.
- Its presence is a malignancy clue, not a reliable indicator of lung tumor subtype.

Cutaneous clues: Avoid overinterpretation

- Acanthosis nigricans can occur in non-neoplastic conditions as well.
- That a subset of cases are cancer-associated.
- Clinical context and temporal onset influence the significance of the finding.
- A paraneoplastic label should not be assigned solely from skin morphology.

Hypertrophic pulmonary osteoarthropathy



Schematic

Three components of hypertrophic osteoarthropathy

- Periosteal new bone forms preferentially along distal long bones and bones of hands and feet.
- Adjacent joints show arthritis.
- Clubbing of fingers or other digits accompanies the syndrome.
- The complete constellation is more informative than clubbing alone.

Where does periosteal bone form?

- Distal portions of long bones.
- Metatarsals and metacarpals are named sites.
- Proximal phalanges may also develop new periosteal bone.
- These osseous changes distinguish osteoarthropathy from an isolated nail change.

Digital clubbing is not identical to osteoarthropathy

Isolated clubbing

- Change in distal digit contour
- Occurs in multiple non-neoplastic disorders
- Does not prove periostitis or cancer

Hypertrophic osteoarthropathy

- Clubbing PLUS periosteal new bone
- Arthritis of adjacent joints
- Distinct paraneoplastic clinical complex

Clubbing has nonmalignant causes

- Diffuse pulmonary diseases may produce finger clubbing.
- Additional associations include congenital cyanotic heart disease and liver disease.
- Inflammatory bowel disease is another listed context.
- Thus, a clubbed digit is not pathognomonic for lung carcinoma.

Mechanism of hypertrophic osteoarthropathy

- The neoplasia chapter describes the cause as unknown.
- Association with lung carcinoma is established; A single causal mediator is not established in the supplied text.
- The lecture should not assign an invented cytokine pathway as proven.
- Pathogenesis and clinical recognition must be presented at different certainty levels.

Case: Clubbing with periosteal changes

Vignette

A patient with a lung tumor develops digital clubbing, painful joints, and new periosteal bone at the distal long bones.

Interpretation

- Recognize the full syndrome rather than clubbing alone.
- Do not ascribe a proven mediator to the syndrome.

Answer

Hypertrophic pulmonary osteoarthropathy; The source does not establish its cause.

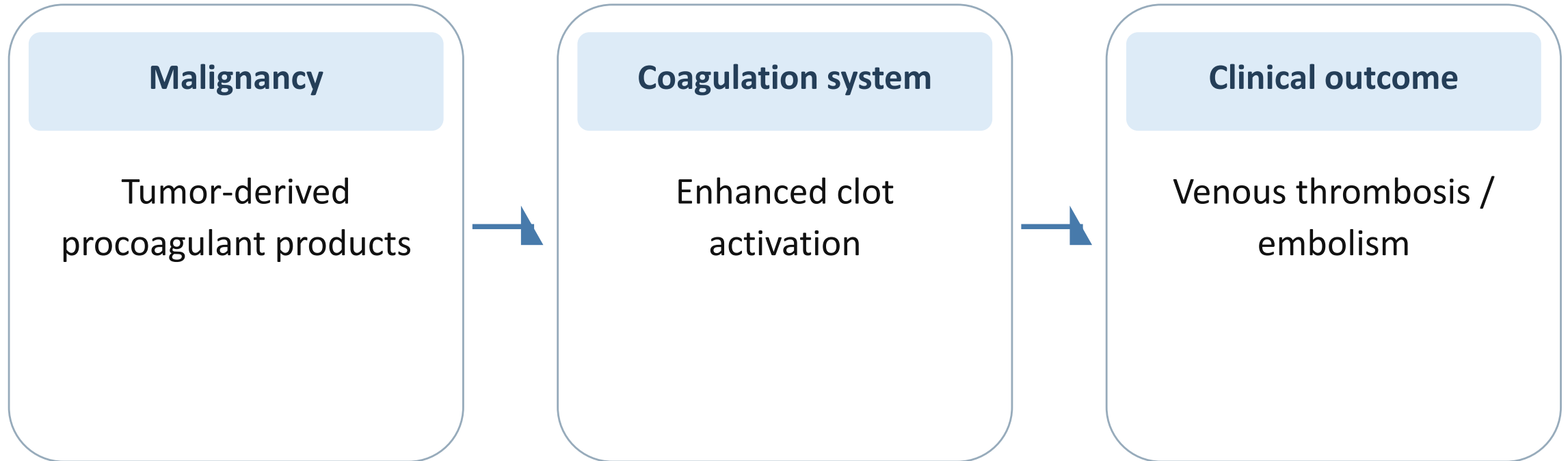
Leukemoid reactions

- Lung carcinoma can be associated with hematologic abnormalities, including leukemoid reactions.
- A leukemoid pattern is a reactive systemic blood-picture abnormality rather than proof of leukemia.
- Its presence belongs to the paraneoplastic differential when local explanations are inadequate.
- The lung chapter does not prescribe a specific mechanism or subtype for this finding.

Cancer-associated hypercoagulability

- Thrombotic events are an important systemic manifestation of cancer.
- Trousseau syndrome is a classic cancer-associated thrombophilic phenotype.
- Lung carcinoma, along with pancreatic and other cancers, may be associated.
- Deep venous thrombosis and thromboembolism may complicate the course.

A paraneoplastic route to thrombosis



Schematic

Trousseau syndrome: Interpretation

- The syndrome classically encompasses migratory thrombophlebitis in cancer.
- Tumor products—including mucins in some cancers—to clotting activation.
- The lung chapter also highlights deep vein thrombosis and thromboembolism.
- Absence of a large tumor burden does not exclude a systemic prothrombotic effect.

Nonbacterial thrombotic endocarditis

- Advanced malignancy may be accompanied by bland fibrinous valve vegetations.
- These lesions are sterile and reflect a hypercoagulable state.
- Left-sided cardiac valves are commonly involved description.
- Vegetation-derived emboli may produce additional systemic complications.

Different vascular effects of cancer

Venous thrombotic events

- Deep venous thrombosis
- Migratory thrombophlebitis
- Potential thromboembolism

Valve-associated thrombotic events

- Sterile fibrinous vegetations
- Nonbacterial thrombotic endocarditis
- Potential systemic embolism

Case: Venous thrombosis and an occult tumor

Vignette

A patient experiences migratory episodes of thrombophlebitis and is later diagnosed with lung carcinoma.

Interpretation

- Interpret the vascular finding as a possible systemic tumor effect.
- Separate a procoagulant syndrome from anatomical venous compression.

Answer

Trousseau phenomenon is a recognized cancer-associated hypercoagulable syndrome.

Organ-system classification at a glance

System	Examples in lung cancer	Typical mechanism
Endocrine	SIADH; Cushing; hypercalcemia	Ectopic tumor mediators
Neurologic	Lambert–Eaton; sensory neuropathy	Often immunologic
Skin / musculoskeletal	Acanthosis; osteoarthropathy	Variable / incompletely known
Vascular / blood	Trousseau; leukemoid reaction	Clotting and host responses

Tumor-subtype associations worth remembering

Primary histology	High-yield association	Limitation
Small cell lung carcinoma	SIADH; ACTH syndrome; Lambert–Eaton	A tendency, not an exclusive rule
Squamous cell carcinoma	Humoral hypercalcemia	Often PTH-related protein
Pulmonary carcinoid	Carcinoid syndrome	Only a subset is functional

A syndrome can reveal an occult lung tumor

- Systemic manifestations can arise before a pulmonary mass is clinically detected.
- The most informative clues combine a characteristic phenotype with a plausible tumor association.
- Examples include Lambert–Eaton, ectopic ACTH syndrome, and inappropriate ADH secretion.
- A compatible syndrome supports investigation; It does not by itself establish malignancy.

Do not confuse paraneoplasia with metastasis

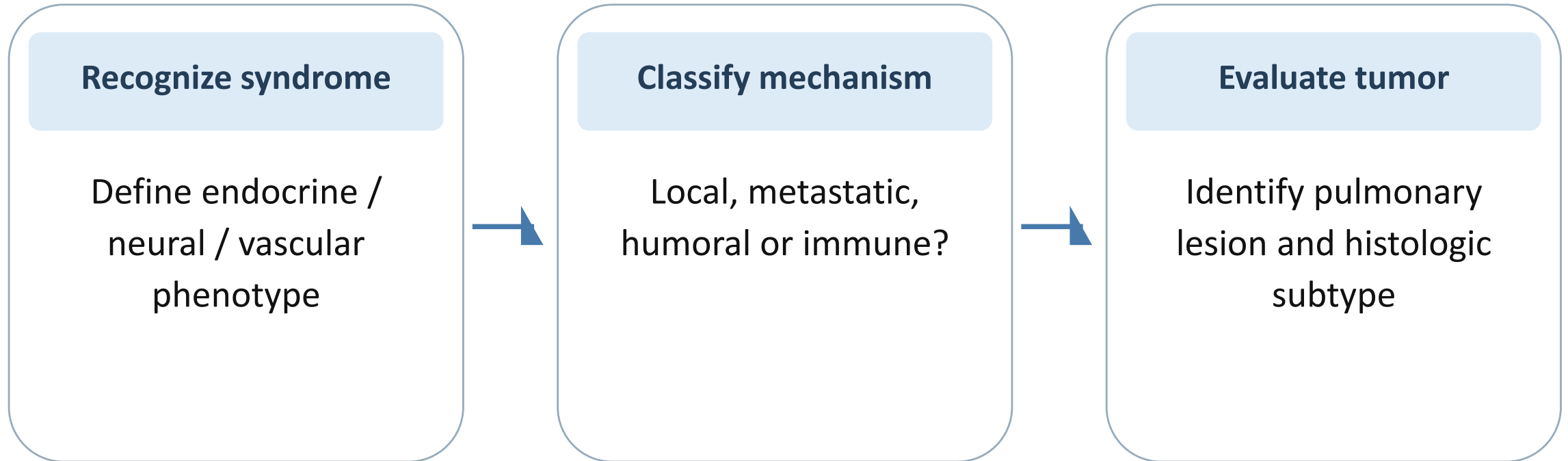
Metastatic effect

- Distant tumor deposit causes local injury
- Bone metastasis causes osteolytic hypercalcemia
- Brain metastasis causes focal neurologic effects

Paraneoplastic effect

- Systemic mediator or immune response
- PTH-related humoral hypercalcemia
- Lambert–Eaton without neural deposits

A pathology-based diagnostic reasoning sequence



Schematic

This is an instructional reasoning schematic, not a formal practice guideline.

Avoid three diagnostic shortcuts

- Do not infer small cell carcinoma solely because a patient has SIADH.
- Do not assume hypercalcemia must reflect bone metastasis.
- Do not label any clubbing as hypertrophic osteoarthropathy.
- Use the clinical phenotype, underlying mechanism and confirmed tumor findings together.

Integrated case: Three clues, three pathways

Vignette

A pulmonary cancer patient develops hyponatremia, episodic muscle weakness that improves after activity, and venous thrombosis.

Interpretation

- Hyponatremia → ectopic ADH / SIADH.
- Facilitating weakness → Lambert–Eaton.
- Venous thrombosis → hypercoagulability.

Answer

One tumor may produce multiple distinct systemic manifestations; Do not force a single mediator to explain all three.

Clinical consequences and prioritization

- Electrolyte disturbances can be clinically significant even if the pulmonary mass is small.
- Neuromuscular dysfunction may be functionally disabling before tumor detection.
- Thromboembolism creates complications independent of thoracic invasion.
- These are not incidental associations: They may alter the immediate clinical problem.

Consolidation: Four pathologic principles

- Ectopic products create remote hormonal phenotypes.
- Autoimmunity can injure a neuromuscular target shared with a tumor.
- Thrombotic and connective-tissue reactions broaden the phenotype beyond hormones.
- Histologic associations aid pattern recognition but are never absolute.

Rapid retrieval: Finding → mechanism

Finding	Most directly supported explanation
Hyponatremia with SIADH	Tumor-derived antidiuretic activity
Cushing syndrome	Ectopic ACTH / ACTH-like peptides
Hypercalcemia without bone destruction	PTH-related humoral substances
Facilitating limb weakness	Presynaptic calcium-channel autoantibodies
Clubbing + periostitis + arthritis	Hypertrophic pulmonary osteoarthropathy

References and source boundaries

- Primary: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 15, pp. 653–659.
- Mechanistic context: Chapter 7, pp. 294–295, including Table 7.11.
- Neuromuscular detail: Chapter 27, pp. 1115–1116.
- Diagnostic algorithms and therapeutic recommendations are outside this source-restricted lecture.