

Paraneoplastic Syndromes

Systemic effects of cancer beyond direct invasion and metastasis

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Learning objectives

- Define a paraneoplastic syndrome and distinguish it from direct tumor effects.
- Relate ectopic secretions, immune responses, and procoagulant products to clinical syndromes.
- Recognize characteristic cancer–syndrome associations across organ systems.
- Use clinicopathologic clues without equating association with definitive diagnosis.

CLINICOPATHOLOGIC POINT

Organize every syndrome by mechanism, phenotype, and associated tumor.

The defining concept

A cancer-associated clinical disorder not readily explained by tumor location or native endocrine function.

- A tumor can produce systemic effects at sites remote from the mass.
- The syndrome may be recognized before the underlying malignancy.
- The mechanism may be secretory, immune, or prothrombotic.

What paraneoplastic does—and does not—mean

Within the definition

- Remote functional consequences of tumor-derived mediators
- Cross-reactive immune injury to normal tissues
- Systemic coagulation activation by tumor products

Different mechanism

- Direct compression or infiltration by a mass
- Metastatic organ destruction or osteolysis
- Ordinary secretion from a tumor's native endocrine lineage

The clinical phenotype alone cannot establish which mechanism is operating.

Why recognition matters

Early clue

May be the initial signal of an otherwise occult cancer.

Serious disease

Can cause major morbidity and sometimes death.

Diagnostic confusion

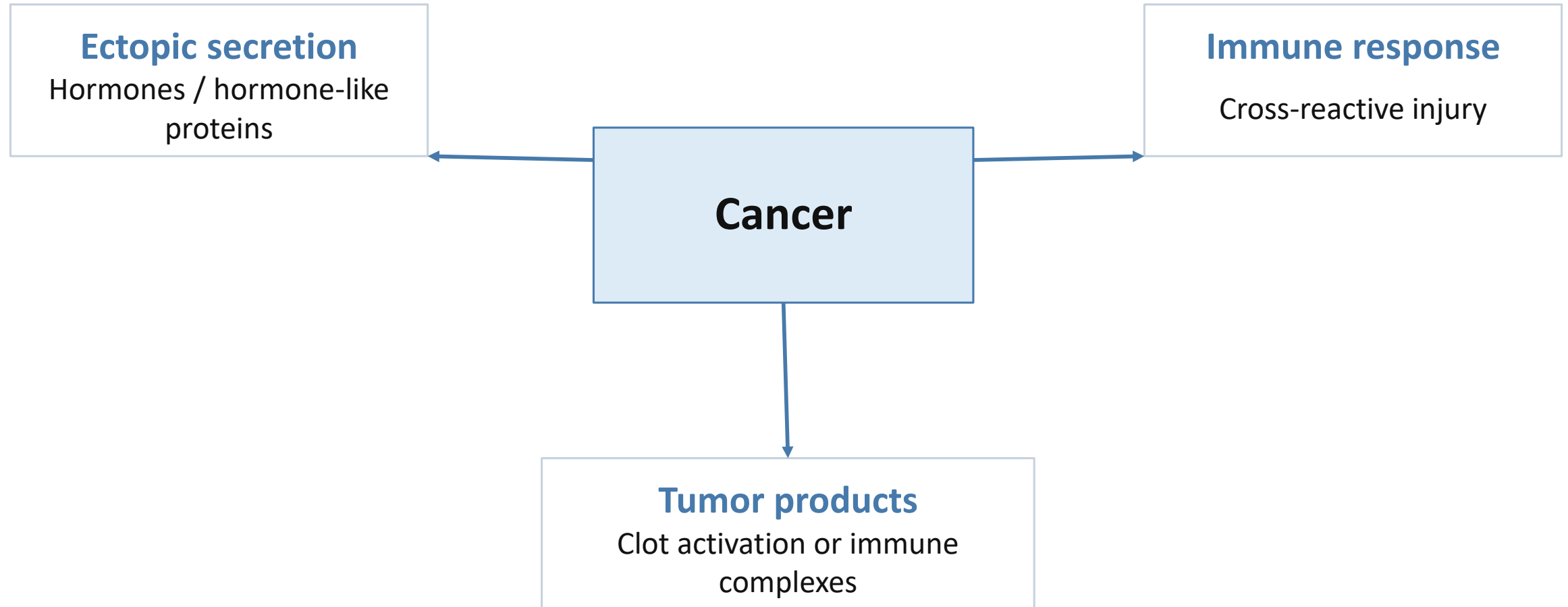
Can imitate metastasis and distort treatment decisions.

Clinical presentation may precede cancer detection



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- The order of presentation may be reversed: Systemic manifestation first, cancer diagnosis later.
 - Finding a characteristic syndrome prompts investigation; It does not prove a particular tumor.

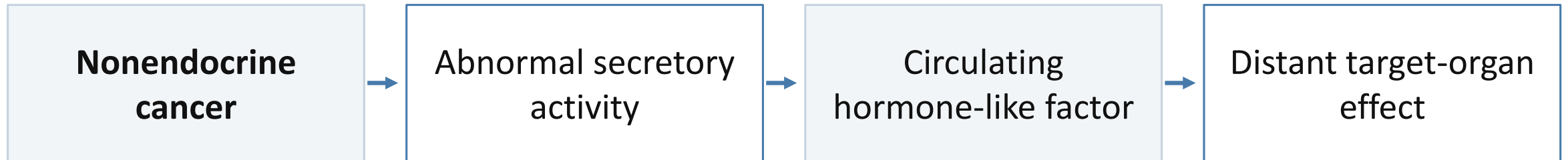
Mechanisms: A unifying overview



Major clinical categories

System	Representative syndromes
Endocrine / metabolic	Cushing syndrome; SIADH; Hypercalcemia; Hypoglycemia; Polycythemia; Osteomalacia
Neuromuscular	Peripheral / CNS dysfunction; Polymyopathy; Myasthenic syndrome
Cutaneous / skeletal	Acanthosis nigricans; Dermatomyositis; Hypertrophic osteoarthropathy
Vascular / other	Trousseau phenomenon; DIC; NBTE; Red cell aplasia; Nephrotic syndrome

Ectopic hormone production



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- The causal secretion is ectopic because the cancer is not of the corresponding endocrine origin.
 - Interpret endocrine manifestations in relation to the tumor's tissue lineage.

Paraneoplastic Cushing syndrome

- Corticotropin (ACTH) or ACTH-like peptides are produced by a nonpituitary neoplasm.
- The source is commonly carcinoma of lung, especially small-cell carcinoma.
- The syndrome represents an ectopic source of a normally pituitary hormone.

CLINICOPATHOLOGIC POINT

The text identifies Cushing syndrome as the most common paraneoplastic endocrinopathy.

ACTH derives from a larger precursor



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- POMC is the large precursor molecule from which corticotropin is derived.
 - Elevated circulating POMC and ACTH in lung-cancer–associated Cushing syndrome.

POMC helps distinguish source patterns

Ectopic ACTH in lung carcinoma

- Circulating ACTH elevated
- Circulating precursor POMC elevated
- Nonpituitary cancer is the secretory source

Pituitary ACTH excess

- Corticotropin excess originates in the pituitary
- POMC is not found in serum in the source comparison
- Anatomic / secretory origin is different

Source-reported distinction; Not a standalone modern diagnostic algorithm.

Tumors linked to ectopic ACTH

Associated tumor table	Clinical association
Small-cell carcinoma of lung	Cushing syndrome
Pancreatic carcinoma	Cushing syndrome
Neural tumors	Cushing syndrome

SIADH as a tumor-associated endocrinopathy

- The syndrome of inappropriate antidiuretic hormone secretion is included among ectopic endocrine effects.
- Small-cell carcinoma of the lung is a principal tumor association.
- Intracranial neoplasms are also listed as associated lesions.

CLINICOPATHOLOGIC POINT

The source table implicates antidiuretic hormone or atrial natriuretic hormones.

Different secretory outputs, different syndromes

ACTH-related phenotype

- Ectopic corticotropin or related peptides
- Cushing syndrome
- Small-cell lung carcinoma is prominent

Antidiuretic hormone–related phenotype

- Inappropriate water-regulating hormone activity
- SIADH clinical syndrome
- Small-cell lung and intracranial tumors listed

Both are endocrine presentations; The secreted mediator determines the target physiology.

Cancer-associated hypercalcemia: Two processes

Local skeletal disease

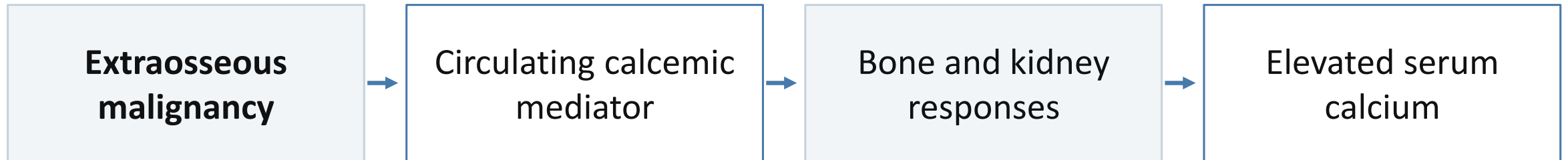
- Osteolysis from primary bone cancer
- Bone destruction by metastases
- Not classified as paraneoplastic in this definition

Humoral effect

- Extraosseous tumor releases calcemic substances
- Systemic calcium regulation is altered
- This pathway is paraneoplastic

Always separate osteolytic disease from humoral hypercalcemia.

The humoral hypercalcemia pathway



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- The systemic mediator pathway does not require tumor infiltration of bone.
 - Parathyroid hormone–related protein (PTHrP) is the major factor discussed.

PTHrP resembles PTH in selected activities

- Parathyroid hormone–related protein (PTHrP) shares partial structural homology with PTH.
- Both ligands bind the same G protein–coupled receptor.
- Their biologic actions overlap, but are not identical.

CLINICOPATHOLOGIC POINT

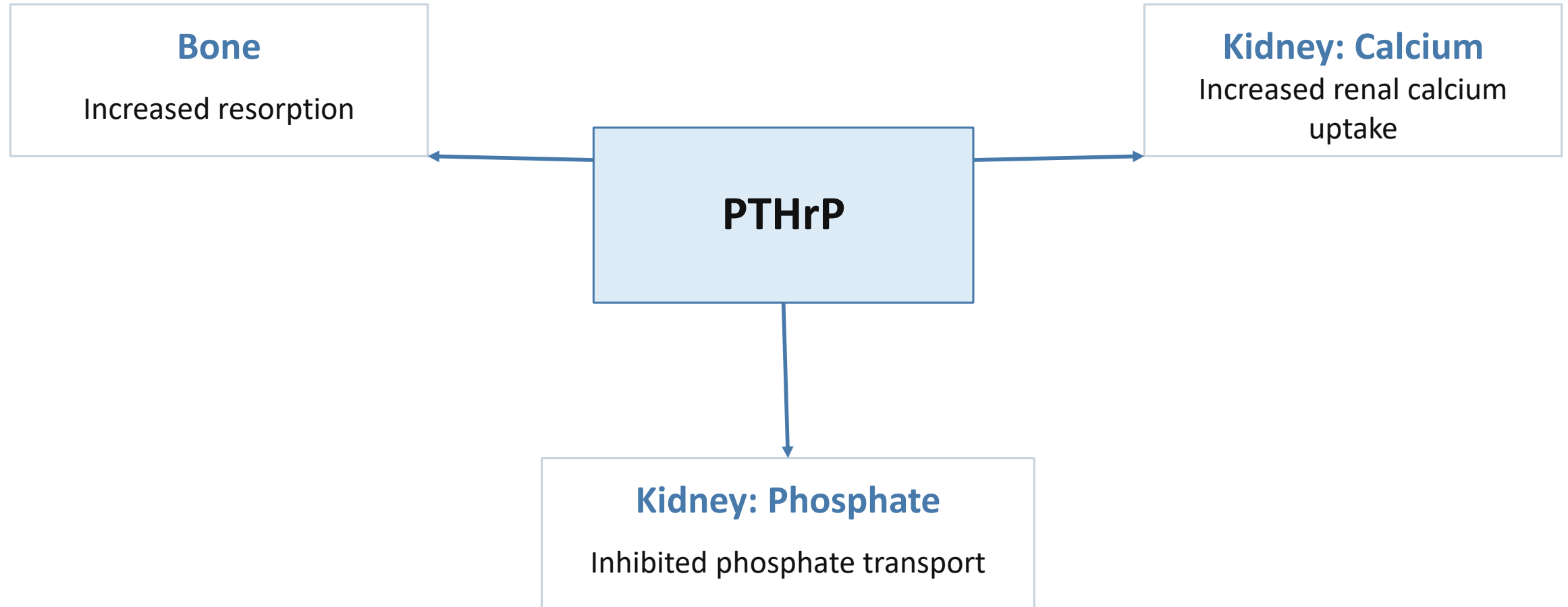
Shared receptor does not mean every physiologic effect is equivalent.

A common PTH / PTHrP receptor



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- Receptor identity explains why ectopic PTHrP can imitate selected effects of PTH.
 - The tumor supplies the ligand; Normal tissues supply the receptors.

How PTHrP raises circulating calcium



PTHrP is not exclusive to cancer

- Small quantities are normally produced by several tissues.
- Normal epithelial cells, including keratinocytes, can produce PTHrP.
- This distribution provides a plausible link to PTHrP-producing squamous cell carcinoma.

CLINICOPATHOLOGIC POINT

Normal expression and tumor-associated excess are distinct biological contexts.

Tumors implicated in humoral hypercalcemia

Cancer association	Clinicopathologic distinction
Squamous cell carcinoma of lung	PTHrP release is a characteristic mechanism
Breast carcinoma	Humoral effect may coexist with osteolytic metastases
Renal and ovarian carcinomas	Both associated with humoral calcium disturbances
Adult T-cell leukemia / lymphoma	Hematolymphoid tumor associated with hypercalcemia

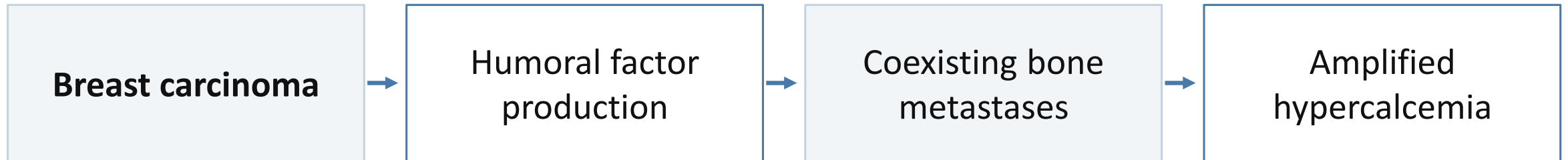
Additional humoral mediators

- Robbins also implicates IL-1, transforming growth factor- α , and tumor necrosis factor.
- Dihydroxyvitamin D is another factor named in the narrative.
- Hypercalcemia in malignancy is therefore not always reducible to a single molecular factor.

CLINICOPATHOLOGIC POINT

The mediator list describes plausible causes—not a ranking of tests or treatment targets.

Mixed mechanisms in breast cancer



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- Bone metastases may exacerbate a paraneoplastic humoral calcium disturbance.
 - Do not label osteolysis itself as paraneoplastic merely because PTHrP is also involved.

Hypercalcemia: Mechanism-based reasoning

CLINICAL PROBLEM

A patient with carcinoma has elevated calcium and osseous metastatic disease. Does “hypercalcemia” alone identify a paraneoplastic syndrome?

INTERPRETATION

No. Osteolysis is a direct tumor effect; A separate circulating calcemic factor is the paraneoplastic pathway.

A patient may have both pathways simultaneously, particularly with breast cancer.

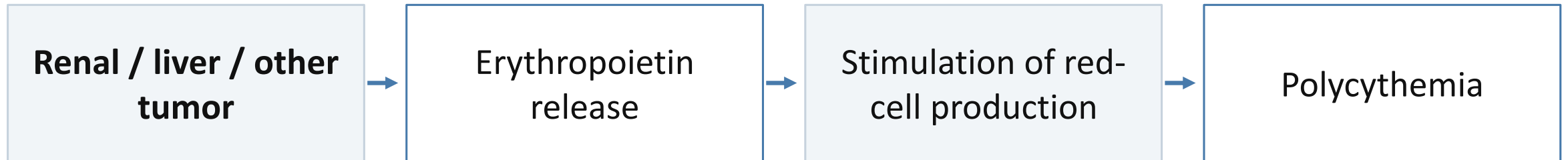
Paraneoplastic hypoglycemia

- The source table links ovarian carcinoma and fibrosarcoma with hypoglycemia.
- Insulin or insulin-like substances are the proposed mediators.
- The mechanism is classified with ectopic tumor-derived metabolic effects.

CLINICOPATHOLOGIC POINT

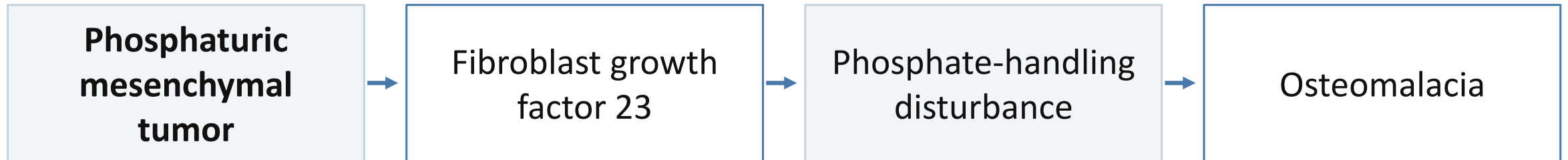
The extracted chapter does not specify a confirmatory laboratory protocol.

Tumor-associated polycythemia



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- Associated tumors in the table: Renal carcinoma, hepatocellular carcinoma, and cerebellar hemangioma.
 - The secretory product—not tumor bulk—explains the hematologic phenotype.

FGF-23 and tumor-associated osteomalacia



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- FGF-23 as the mediator of this distinctive syndrome.
 - This is a bone disorder arising from a circulating tumor product, not skeletal invasion.

Endocrine syndrome-to-mediator map

Clinical syndrome	Proposed mediator	Illustrative tumor
Cushing syndrome	ACTH / ACTH-like	Small-cell lung carcinoma
SIADH	ADH / natriuretic hormones	Small-cell lung carcinoma
Hypercalcemia	PTHrP and other factors	Squamous lung carcinoma
Polycythemia	Erythropoietin	Renal carcinoma
Osteomalacia	FGF-23	Phosphaturic mesenchymal tumor

One cancer can produce different syndromes

CLINICAL PROBLEM

Small-cell lung carcinoma is associated with Cushing syndrome and SIADH in the same source table. What determines the syndrome?

INTERPRETATION

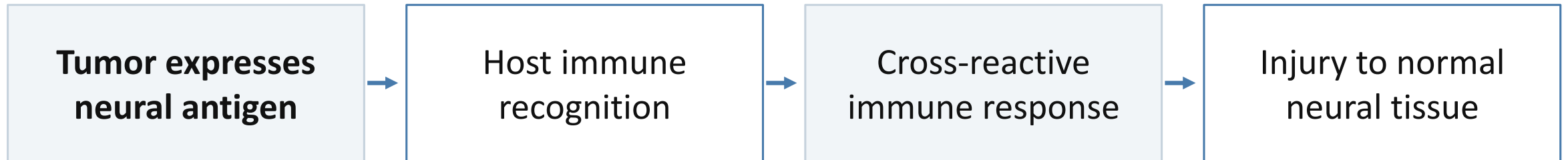
The tumor-associated secretory product and its target-organ effects—not simply the primary tumor site.

The same histologic cancer category may be linked to different systemic presentations.

Neuromyopathic syndrome spectrum

Anatomic / functional pattern	Examples
Peripheral nervous system	Peripheral neuropathies
Central nervous system	Encephalitis; Cortical cerebellar degeneration
Skeletal muscle	Polymyopathy resembling polymyositis
Neuromuscular transmission	Myasthenic syndrome resembling myasthenia gravis

Immune cross-reactivity: Proposed sequence



-
- Tumor expression of antigens normally restricted to the neuromuscular system is proposed as an initiating event.
 - The text treats this model as plausible; Mechanisms remain incompletely understood.

Cellular and humoral immune effectors

T-cell–associated mechanisms

- Immune responses frequently involve T cells
- Tissue injury may reflect immune-cell attack
- The cross-reactive target is host tissue

Antibody-associated mechanisms

- Cross-reactive neuronal antibodies occur in some syndromes
- Antibodies may recognize neuronal antigens
- Detection is not described as universal

Avoid assuming one antibody-mediated mechanism for all neurologic syndromes.

Peripheral neuropathy as a remote effect

- Peripheral neuropathies are among the neuromyopathic manifestations.
- A remote immune process can affect nerves without local tumor invasion.
- Direct nerve compression and metastatic involvement remain distinct mechanisms to exclude.

CLINICOPATHOLOGIC POINT

Neuropathy is a presentation category, not proof of a particular cancer.

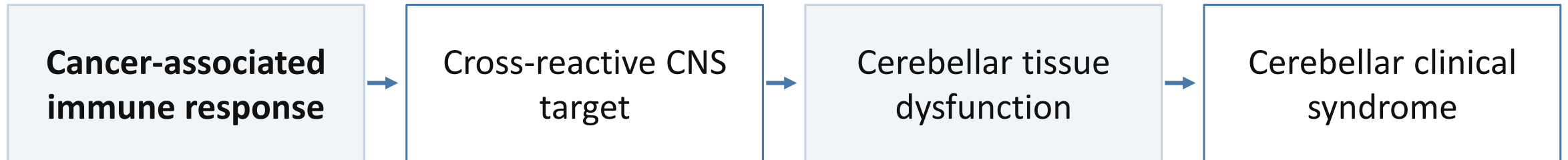
Encephalitis in cancer-associated immunity

- Encephalitis appears in the source list of paraneoplastic neurologic syndromes.
- The immunologic model explains CNS injury in the absence of direct tumor spread.
- Anatomic localization of dysfunction is separate from localization of the malignancy.

CLINICOPATHOLOGIC POINT

The source excerpt does not specify named encephalitic antibody subtypes.

Paraneoplastic cerebellar degeneration



- Cortical cerebellar degeneration among the neuromyopathic forms.
- The flowchart is a conceptual interpretation, not a microscopic description.

A polymyopathy resembling polymyositis

- Cancer-associated muscular dysfunction may resemble polymyositis.
- The source groups this with probable immune-mediated neuromyopathic syndromes.
- A muscle-centered phenotype can be paraneoplastic despite an extra-muscular primary tumor.

CLINICOPATHOLOGIC POINT

Similar clinical patterns do not establish identical etiology.

Myasthenic syndrome: Phenotype versus cause

Observed resemblance

- Myasthenic syndrome resembles myasthenia gravis
- Neuromuscular dysfunction is prominent
- The clinical pattern directs evaluation

Paraneoplastic attribution

- A neoplasm-associated immunologic mechanism is proposed
- Not explained merely by tumor mass
- Bronchogenic and thymic tumors in its myasthenia row

The source does not provide subtype-specific electrophysiologic criteria.

Direct neurologic injury versus paraneoplastic

Direct or metastatic

- Mass effect in neural tissue
- Structural infiltration or compression
- Neurologic localization may match a tumor deposit

Paraneoplastic / immune

- Immune response directed against host antigens
- Remote organ dysfunction
- A primary cancer may be anatomically distant

The distinction changes interpretation of neurologic findings in oncology.

Reasoning exercise: A neurologic clue

CLINICAL PROBLEM

A patient develops a progressive neurologic syndrome and later is found to have breast carcinoma. Is the neurologic syndrome necessarily metastatic?

INTERPRETATION

No. Breast carcinoma is linked to neurologic paraneoplastic disorders; Determine the mechanism rather than assuming metastasis.

The original source specifically warns that paraneoplastic syndromes can mimic spread of cancer.

Cutaneous manifestations

Manifestation	Tumor associations in source	Mechanism stated
Acanthosis nigricans	Gastric, lung, uterine carcinoma	Immune / EGF-associated
Dermatomyositis	Bronchogenic and breast carcinoma	Immunologic
Leser–Trélat sign	May accompany acanthosis nigricans	Association / temporal clue

Acanthosis nigricans: Recognizable morphology

Gray-black, thickened, hyperkeratotic plaques with a velvety surface.

- The morphology is cutaneous, although the associated cancer may be visceral.
- Texture and color are part of the clinical description.
- The source notes gastric carcinoma particularly often among associated cancers.

Acanthosis nigricans is not always malignant

Nonmalignant setting

- Can occur as a genetically determined condition
- May be seen in juveniles or adults
- Phenotype alone is insufficient

Paraneoplastic setting

- Described with several carcinomas
- The source emphasizes adult presentations, especially after age 40
- May arise before cancer detection

An approximate cancer association in about half of the cases considered; Context matters.

Leser–Trélat sign

- Describes abrupt appearance of multiple seborrheic keratoses.
- Can occur alongside acanthosis nigricans.
- The skin eruption may precede recognition of an underlying cancer.

CLINICOPATHOLOGIC POINT

A temporal association is a clinical clue; It is not tumor histology.

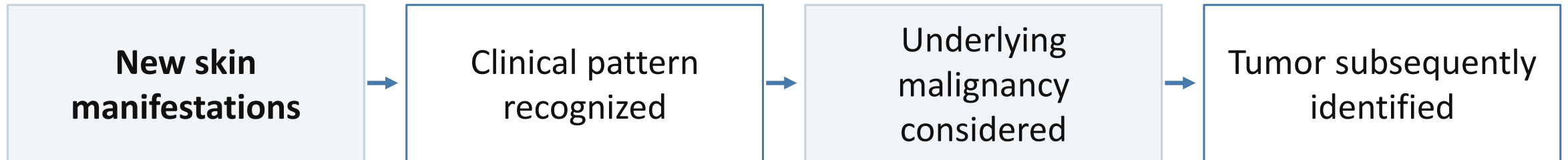
Dermatomyositis as a paraneoplastic clue

- Dermatomyositis is included as an immunologic dermatologic manifestation.
- Bronchogenic and breast carcinomas are listed associations.
- In this context, the cutaneous and muscle phenotype requires separation from direct cancer effects.

CLINICOPATHOLOGIC POINT

The table does not specify a particular autoantibody or diagnostic sensitivity.

Cutaneous findings can reverse the sequence of diagnosis



-
- That acanthosis-associated changes may appear before cancer is discovered.
 - Timing is clinically informative but does not itself prove causality.

Hypertrophic osteoarthropathy: Defining triad

Periostosis

New bone deposition along distal long bones and small tubular bones.

Arthritis

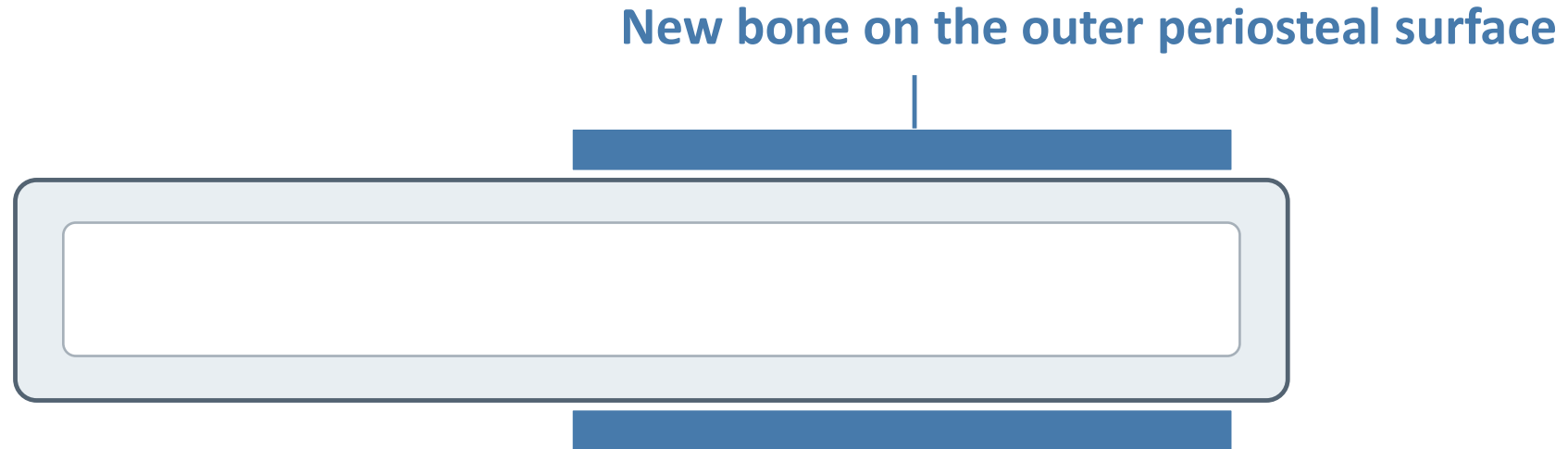
Inflammation or symptoms at adjacent joints.

Clubbing

Enlargement / characteristic change of distal digits.

Where the bone change occurs

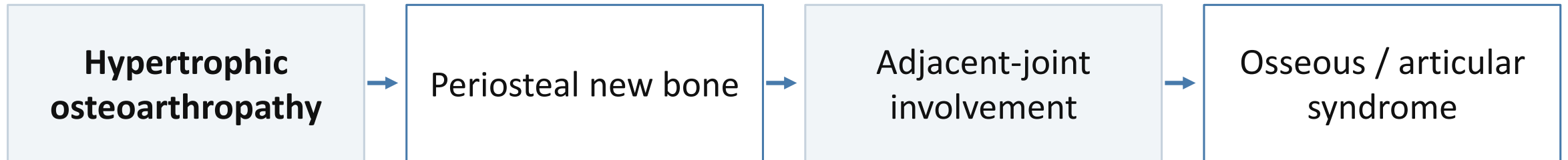
Schematic



- Periosteal new bone formation
- Distal long bones
- Metatarsals, metacarpals and proximal phalanges

Native schematic of bone surface apposition; Not a radiograph or histologic specimen.

Periosteal bone change and joint symptoms



- The skeletal pattern links distal periosteal deposition with arthritis of adjacent joints.
- Bone involvement here reflects systemic change, not necessarily metastatic deposits.

Clubbing is not cancer-specific

Neoplastic association

- Bronchogenic carcinoma
- Thymic neoplasms
- May occur within hypertrophic osteoarthropathy

Noncancer associations

- Diffuse pulmonary and liver disease
- Congenital cyanotic heart disease
- Ulcerative colitis and other disorders

Clubbing can be present without full osteoarthropathy.

Osteoarthropathy: Association and uncertainty

- Hypertrophic osteoarthropathy in 1%–10% of lung carcinoma cases.
- The syndrome is less often associated with other cancers.
- Its cause is described as unknown in this source.

CLINICOPATHOLOGIC POINT

Do not assign an unverified molecular mechanism to this classic morphologic triad.

Vascular manifestations: Three different lesions

Disorder	Primary pathologic process
Trousseau phenomenon	Migratory venous thrombophlebitis
Disseminated intravascular coagulation	Generalized intravascular activation of clotting
Nonbacterial thrombotic endocarditis	Bland fibrinous vegetations on valve leaflets

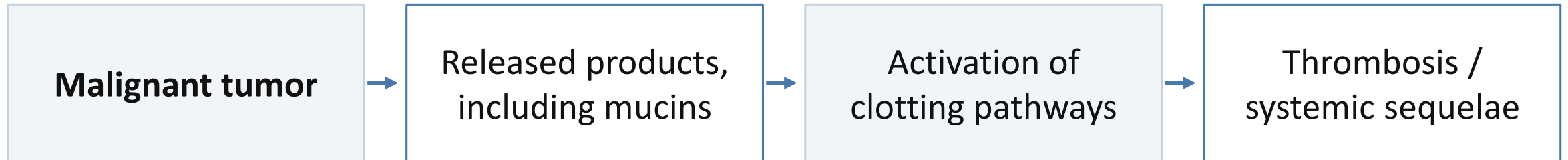
Trousseau phenomenon

- Migratory thrombophlebitis is associated with deep-seated cancers.
- Pancreatic carcinoma is a prominent source association.
- Lung carcinoma and other cancers are also implicated.

CLINICOPATHOLOGIC POINT

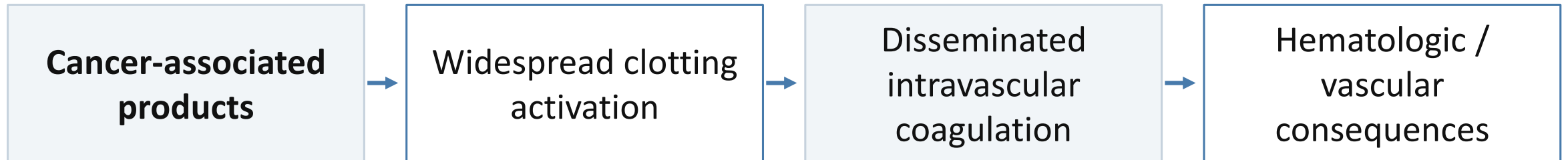
The syndrome is a manifestation of cancer-associated hypercoagulability.

Tumor products can activate clotting



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- Mucins are an example listed in the source—not a universal mechanism.
 - The thrombotic clinical syndrome is remote from the tumor's anatomic site.

Disseminated intravascular coagulation



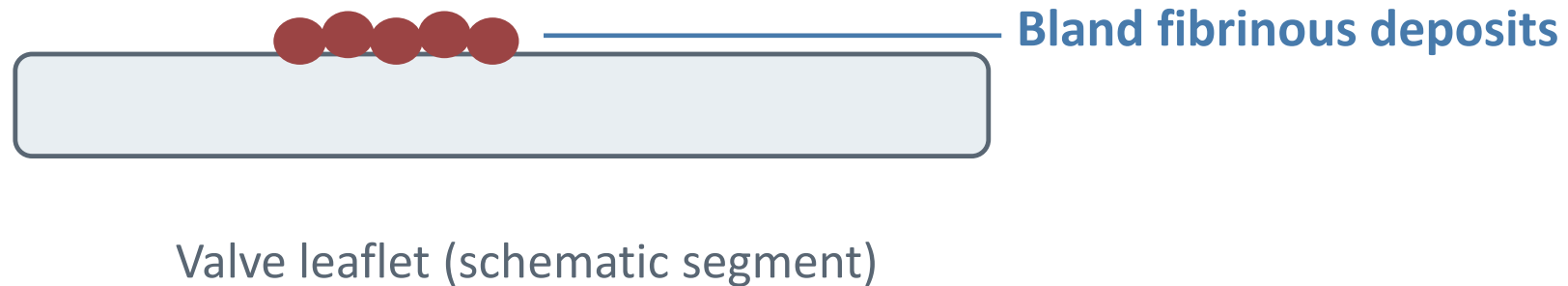
-
- The excerpt places DIC among malignant vascular syndromes.
 - The source table associates it particularly with selected cancers.

Malignancies prominent in DIC

Neoplasm	Syndrome association
Acute promyelocytic leukemia	Disseminated intravascular coagulation
Prostatic adenocarcinoma	Disseminated intravascular coagulation

Nonbacterial thrombotic endocarditis

Schematic



Bland, small, noninfective fibrinous vegetations form on cardiac valve leaflets, often on left-sided valves.

Potential source of emboli

Why valve vegetations matter



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- The source highlights advanced mucin-secreting adenocarcinomas.
 - Embolization adds a distinct complication beyond the underlying cancer.

Distinguishing three prothrombotic patterns

Syndrome	Main site / pattern	Clinical interpretation
Trousseau	Migrating venous thrombophlebitis	Cancer-linked venous thrombosis
DIC	Diffuse intravascular coagulation	Systemic clotting activation
NBTE	Cardiac valvular fibrin deposits	Potential source of emboli

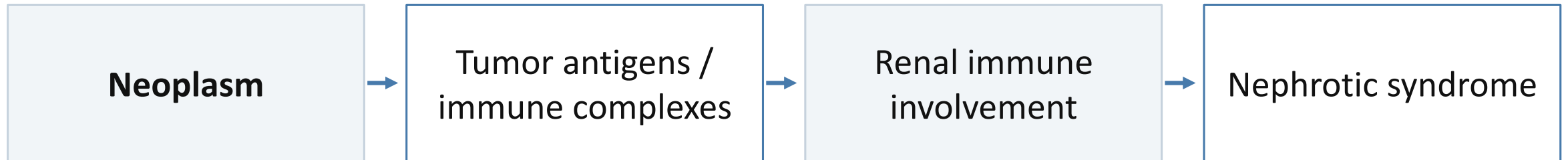
Paraneoplastic red cell aplasia

- Red cell aplasia is included among hematologic paraneoplastic syndromes.
- Thymic neoplasms and large granular lymphocytic leukemia are listed associations.
- An immunologic mechanism is proposed.

CLINICOPATHOLOGIC POINT

Distinct from erythropoietin-associated polycythemia: Opposite hematologic phenotypes.

Nephrotic syndrome in patients with cancer



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- Nephrotic syndrome in association with various cancers.
 - The table invokes tumor antigens and immune complexes as possible mediators.

The same organ system may show opposing outcomes

Red-cell excess

- Polycythemia
- Erythropoietin as secreted mediator
- Renal, hepatic, cerebellar tumors listed

Red-cell failure

- Pure red cell aplasia
- Presumed immunologic process
- Thymic neoplasms / large granular lymphocytic leukemia

Mechanism is more informative than the label “hematologic paraneoplastic.”

Tumor–syndrome associations are patterns, not proofs

- The Robbins table presents major forms of associated cancer, not exhaustive lists.
- One syndrome may accompany several unrelated tumors.
- One tumor type may be linked to several different paraneoplastic phenotypes.
- Attribution requires excluding direct effects and competing causes.

CLINICOPATHOLOGIC POINT

Use the association to guide hypotheses—not to conclude a specific diagnosis from one sign.

Integrated recognition framework



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- Classify: Secretory, immune-mediated, skeletal/dermatologic, or thrombotic.
 - Then match with tumor association and the temporal clinical context.

Application: Endocrine phenotype

CLINICAL PROBLEM

A lung tumor is associated with elevated ACTH and POMC in the circulation. Which paraneoplastic mechanism best fits?

INTERPRETATION

Ectopic ACTH-related Cushing syndrome, classically associated with small-cell carcinoma.

The precursor relationship and lung-cancer association are both explicit.

Application: Distal bone and joint findings

CLINICAL PROBLEM

A person with lung cancer develops finger clubbing, distal periosteal new bone formation, and adjacent-joint arthritis. What syndrome links the findings?

INTERPRETATION

Hypertrophic osteoarthropathy.

The three findings form its defining clinicopathologic triad. The exact cause remains unknown in the excerpt.

Application: Migratory venous thrombosis

CLINICAL PROBLEM

A patient with a deep-seated pancreatic carcinoma experiences migratory thrombophlebitis. What paraneoplastic pattern is illustrated?

INTERPRETATION

Trousseau phenomenon, a cancer-associated hypercoagulable syndrome.

The source connects tumor products such as mucins with activation of clotting.

Application: A CNS syndrome before tumor discovery

CLINICAL PROBLEM

A neurologic presentation appears before any malignancy is known. How might this still be cancer-related?

INTERPRETATION

An occult tumor could trigger a cross-reactive immune response to neural antigens.

The manifestation may precede cancer detection and should not automatically be interpreted as metastatic disease.

Synthesis: Organize by causal mechanism

Dominant mechanism	Illustrative presentation
Ectopic secretion	Cushing syndrome; Hypercalcemia; Polycythemia; Osteomalacia
Immune injury	Neuromyopathic syndromes; Dermatomyositis; Red cell aplasia
Procoagulant products	Trousseau phenomenon; DIC; NBTE
Other / less certain	Hypertrophic osteoarthropathy; Acanthosis nigricans

Four final clinicopathologic principles

- Paraneoplastic manifestations are not synonymous with metastatic disease.
- A circulating mediator or immune response may explain a distant organ phenotype.
- Specific combinations of syndromes and tumor types provide diagnostic clues.
- The mechanism and degree of causal certainty must be stated explicitly.

CLINICOPATHOLOGIC POINT

For any remote cancer-associated sign, determine whether a secretory, immune, or procoagulant process is supported.