

Neuropathies Associated With Malignancy

Mechanisms • nerve-injury patterns • clinicopathologic localization

Peripheral nerve pathology

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Learning objectives

- Classify cancer-associated neuropathies by mechanism rather than tumor label alone.
- Localize symptoms to nerve, plexus, root, or sensory neuron.
- Explain immune and paraprotein-associated axonal or myelin injury.
- Distinguish direct tumor effects from toxicity associated with cancer treatment.

Four principal mechanisms

Cancer-associated peripheral neuropathy

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graph TD; A[Cancer-associated peripheral neuropathy] --> B[Local tumor effect]; A --> C[Paraneoplastic]; A --> D[Paraprotein-mediated]; A --> E[Treatment-related]; B --> B1[Nerve or root compression and infiltration]; C --> C1[Immune injury remote from the tumor]; D --> D1[Tumor-derived immunoglobulins or light chains]; E --> E1[Drug-related nerve injury];
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Local tumor effect

Nerve or root
compression and
infiltration

Paraneoplastic

Immune injury remote
from the tumor

Paraprotein-mediated

Tumor-derived
immunoglobulins or
light chains

Treatment-related

Drug-related nerve
injury

What part of the peripheral nerve is injured?

Axon



Disrupted axon

Primary degeneration; Lower
action-potential amplitude

Myelin / Schwann cell



Myelin gaps

Segmental myelin injury;
Slowed conduction

Neuron cell body



Cell body loss

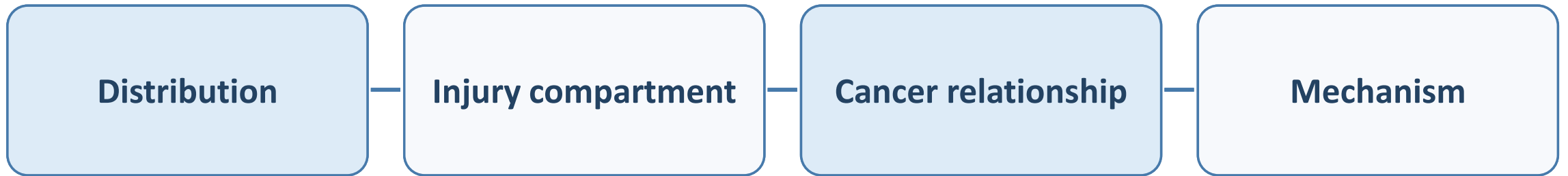
Loss of neuron; Distal
processes degenerate

A phenotype is not a mechanism

Pattern → localization → mechanism

- The same clinical pattern can arise through different pathogenic routes.
- Cancer can affect axons, Schwann-cell myelin, or neuronal cell bodies.
- Begin with anatomic localization, then assess plausible malignant mechanisms.

From anatomy to a cancer-related hypothesis



A focal palsy and a generalized polyneuropathy need different localization.

The mechanism may be direct, paraneoplastic, paraprotein-mediated, or toxic.

Mononeuropathy: A single-nerve deficit

**ONE NERVE
→
RESTRICTED DEFICIT**

- A focal deficit follows the anatomy of the involved nerve.
- Direct tumor infiltration or compression commonly causes axonal mononeuropathy.
- A focal neuropathy may be the presenting symptom of a malignancy.

Polyneuropathy: Multiple nerves

MULTIPLE NERVES
→
OFTEN SYMMETRIC

- Classic length-dependent patterns begin distally and progress proximally.
- Axonal sensorimotor neuropathy is a common paraneoplastic phenotype.
- A treatment-related injury can also affect multiple peripheral nerves.

Axonopathy versus neuronopathy

Axonal neuropathy

- Primary injury occurs in the axonal process.
- In many settings the longest axons are most susceptible.
- Axonal dropout produces reduced response amplitudes.

Sensory neuronopathy

- Primary injury occurs at neuronal cell bodies.
- Affected distal and proximal processes degenerate secondarily.
- A non-length-dependent pattern is possible.

Axonal versus demyelinating physiology

Axonal injury

- Loss of functioning axons lowers recorded signal amplitude.
- Conduction velocity may be relatively preserved.

Demyelinating injury

- Loss of myelin disrupts saltatory conduction.
- Slowed conduction velocity is a hallmark.

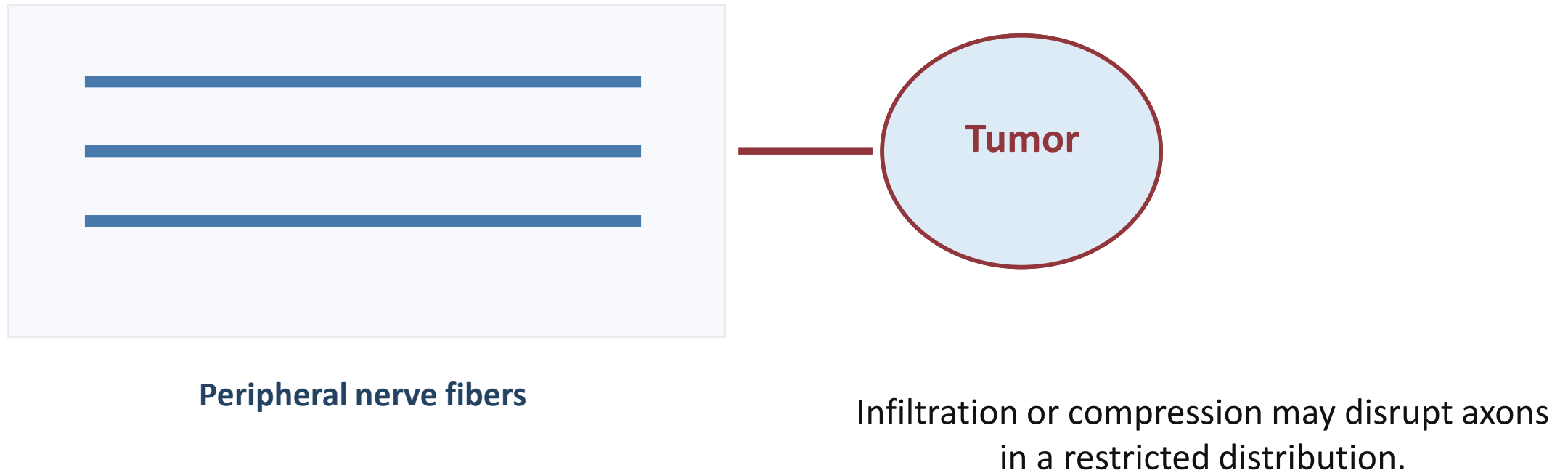
Direct effects: Malignant injury at the nerve

Localized pathology can produce a localized neurologic syndrome.

- Tumor cells may infiltrate a nerve or adjacent tissue may compress it.
- The resulting deficit often follows a single nerve or plexus distribution.
- Some patients first present with a neuropathy before cancer is recognized.

Conceptual anatomy of tumor-related nerve injury

Illustrative direct-effect anatomy (not a specimen)



Lung apex: Brachial plexopathy

APICAL LUNG TUMOR



BRACHIAL PLEXUS

- A neoplasm at the lung apex can affect the nearby brachial plexus.
- The syndrome is a plexopathy rather than a generalized polyneuropathy.
- The exact clinical distribution depends on the injured plexus components.

Pelvic malignancy: Obturator nerve palsy

PELVIC TUMOR
↓
OBTURATOR NERVE

- Pelvic malignant neoplasms may compromise the obturator nerve.
- The resulting focal palsy maps to the anatomy of this nerve.
- Localization is a stronger first clue than assuming a diffuse toxic process.

Cranial neuropathy and skull-base disease

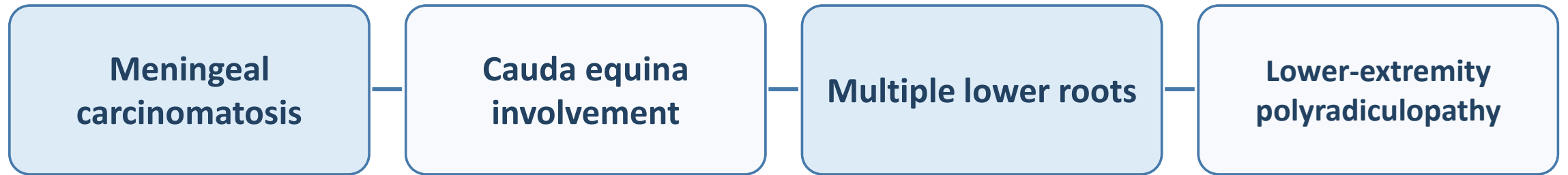
**INTRACRANIAL /
SKULL-BASE TUMOR**



CRANIAL NERVE

- Tumors in the cranial cavity or at the skull base may cause cranial nerve palsies.
- A focal cranial neuropathy warrants assessment of anatomic tumor effects.
- Cancer-associated cranial nerve findings do not automatically establish paraneoplasia.

Meningeal carcinomatosis and cauda equina



Root-level involvement differs anatomically from a solitary peripheral-nerve lesion.

Direct effects: Anatomic localization

Malignant setting	Affected structure	Neuropathy pattern
Apical lung neoplasm	Brachial plexus	Plexopathy
Pelvic malignancy	Obturator nerve	Focal nerve palsy
Intracranial / skull-base tumor	Cranial nerve	Cranial nerve palsy
Meningeal carcinomatosis	Cauda equina roots	Lower-extremity polyradiculopathy

Neurolymphomatosis: A specific infiltrative entity

**LYMPHOMA CELLS
INFILTRATE
PERIPHERAL NERVES**

- Neurolymphomatosis is tumor-cell infiltration of peripheral nerves.
- It is an example of direct malignant nerve injury, not a paraneoplastic syndrome.
- The disease need not present with a known systemic lymphoma.

Neurolymphomatosis: Tumor association

Peripheral nerve infiltration is part of the neoplastic process.

- Most cases arise in association with non-Hodgkin B-cell lymphoma.
- The pathologic principle is direct nerve infiltration by neoplastic cells.
- The infiltrative mechanism distinguishes it from an antibody-mediated neuropathy.

Neurolymphomatosis may precede lymphoma recognition

**NO KNOWN
SYSTEMIC LYMPHOMA
AT PRESENTATION**

- Approximately half have no recognized systemic lymphoma at diagnosis.
- An unexplained neuropathy therefore does not exclude nerve-infiltrating lymphoma.
- This frequency is specific to neurolymphomatosis in the cited textbook.

Local neoplastic neuropathies: Two mechanisms

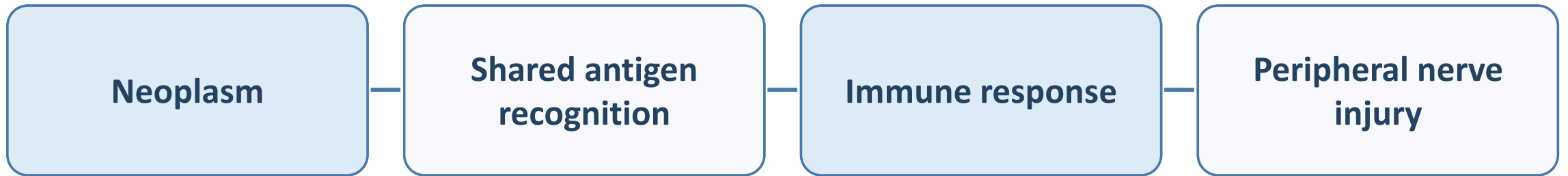
Compression

- Tumor imposes pressure on neural structures.
- Localization reflects the compressed nerve, plexus, or root.

Infiltration

- Tumor cells enter nerve tissue itself.
- Neurolymphomatosis is a specific example.

What makes a neuropathy paraneoplastic?



Neuropathy arises at a distance from direct tumor infiltration or compression.

Paraneoplastic neuropathy may be an early clue

NEUROPATHY CAN PRECEDE CANCER DIAGNOSIS

- A paraneoplastic neuropathy may arise at any point in the cancer course.
- It often appears before the underlying tumor is diagnosed.
- A negative prior cancer history therefore does not rule out a paraneoplastic process.

Paraneoplastic clinical spectrum

Immune-related neuropathy

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graph TD; A[Immune-related neuropathy] --> B[Axonal]; A --> C[Sensory neuronopathy]; A --> D[Demyelinating]; A --> E[Other localizations]; B --> F[Sensorimotor axonal neuropathy]; C --> G[Pure sensory neuronal injury]; D --> H[CIDP-like polyneuropathy]; E --> I[Plexopathy or autonomic neuropathy];
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Axonal

Sensorimotor axonal
neuropathy

Sensory neuronopathy

Pure sensory neuronal
injury

Demyelinating

CIDP-like
polyneuropathy

Other localizations

Plexopathy or
autonomic neuropathy

Sensorimotor axonal neuropathy

Most frequent paraneoplastic phenotype: Sensorimotor axonal.

- It is the most common paraneoplastic neuropathy form.
- Both sensory and motor functions may be affected.
- Axonal injury is the pathologic classification; It is not proof of one tumor type.

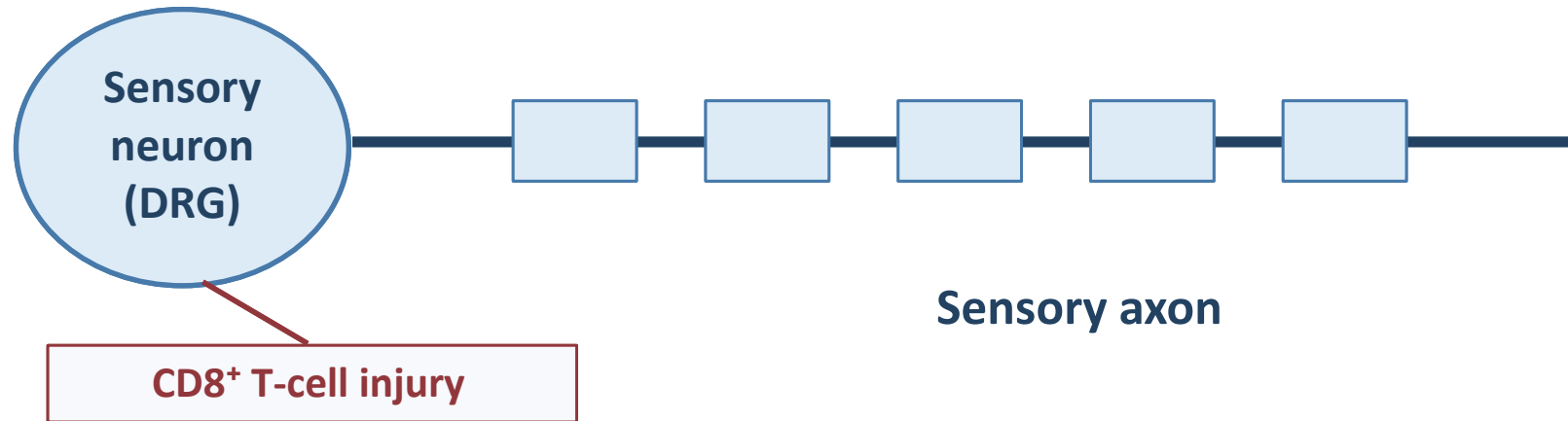
Pure sensory neuronopathy

SENSORY NEURON CELL BODY INJURY

- The primary target is the sensory neuronal cell body, not merely distal myelin.
- Secondary damage extends to axonal processes.
- This localization can explain a multifocal, asymmetric sensory presentation.

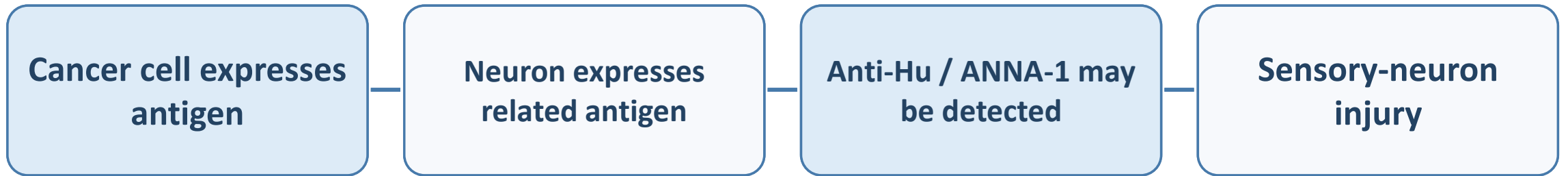
Paraneoplastic sensory neuronopathy: Cellular target

Schematic: Neuronal body injury propagates into its peripheral process



Paraneoplastic sensory neuronopathy: CD8⁺ T-cell attack directed at DRG cells.

Anti-Hu: Tumor–neuron antigen overlap



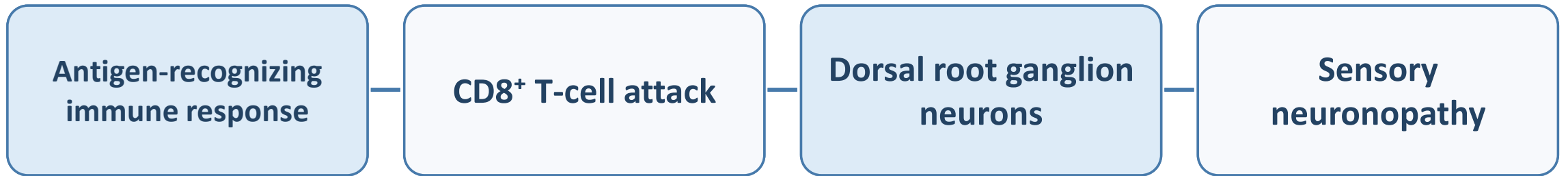
Anti-Hu is a recognized associated autoantibody, not necessarily the direct effector of injury.

Anti-Hu: Terminology and meaning

Antibody association ≠ proven antibody-mediated cytotoxicity.

- Anti-Hu is also called antineuronal nuclear antibody type 1 (ANNA-1).
- It recognizes antigenic proteins expressed in both tumor cells and normal neurons.
- It is often found in paraneoplastic sensory neuronopathy but should not be equated with the full injury mechanism.

Proposed effector: CD8⁺ cytotoxic T cells



Injury as appearing to be mediated by cytotoxic T cells.

Small cell lung carcinoma association

SENSORY NEURONOPATHY
↔
SMALL CELL LUNG CANCER

- Paraneoplastic sensory neuronopathy is most commonly associated with small cell lung cancer.
- The association is not a claim that all sensory neuropathies indicate this cancer.
- Clinical pattern and tumor search must still be interpreted together.

Sensory symptom distribution

Distal onset does not guarantee symmetric dying-back axonopathy.

- Sensory symptoms often begin distally.
- The early pattern may be asymmetric and multifocal.
- Such a pattern differs from a stereotypical symmetric length-dependent polyneuropathy.

Anti-CV2 targets CRMP5

ANTI-CV2 RECOGNIZES CRMP5

- CRMP5 is described as an intracellular signaling protein.
- Anti-CV2 is a distinct paraneoplastic antibody association from anti-Hu.
- The associated neuropathy phenotype matters when interpreting the antibody.

Anti-CV2-associated neuropathy phenotype

Painful + asymmetric + sensorimotor + axonal.

- The typical presentation described is painful and asymmetric.
- Sensory and motor involvement coexist.
- Axonal damage characterizes the peripheral-nerve injury pattern.

Anti-Hu and anti-CV2: Compare the associations

Characteristic	Anti-Hu / ANNA-1	Anti-CV2 / CRMP5
Antigen association	Shared tumor / neuronal proteins	CRMP5 intracellular signaling protein
Reported phenotype	Often sensory neuronopathy	Painful asymmetric sensorimotor axonopathy
Injury explanation	CD8 ⁺ T-cell injury appears important	Autoantibody association described; precise mechanism not specified

Paraneoplastic phenotypes beyond axonopathy

CIDP-like demyelination

- Chronic inflammatory demyelinating polyneuropathy may be paraneoplastic.
- Demyelination affects Schwann-cell myelin.

Plexus or autonomic injury

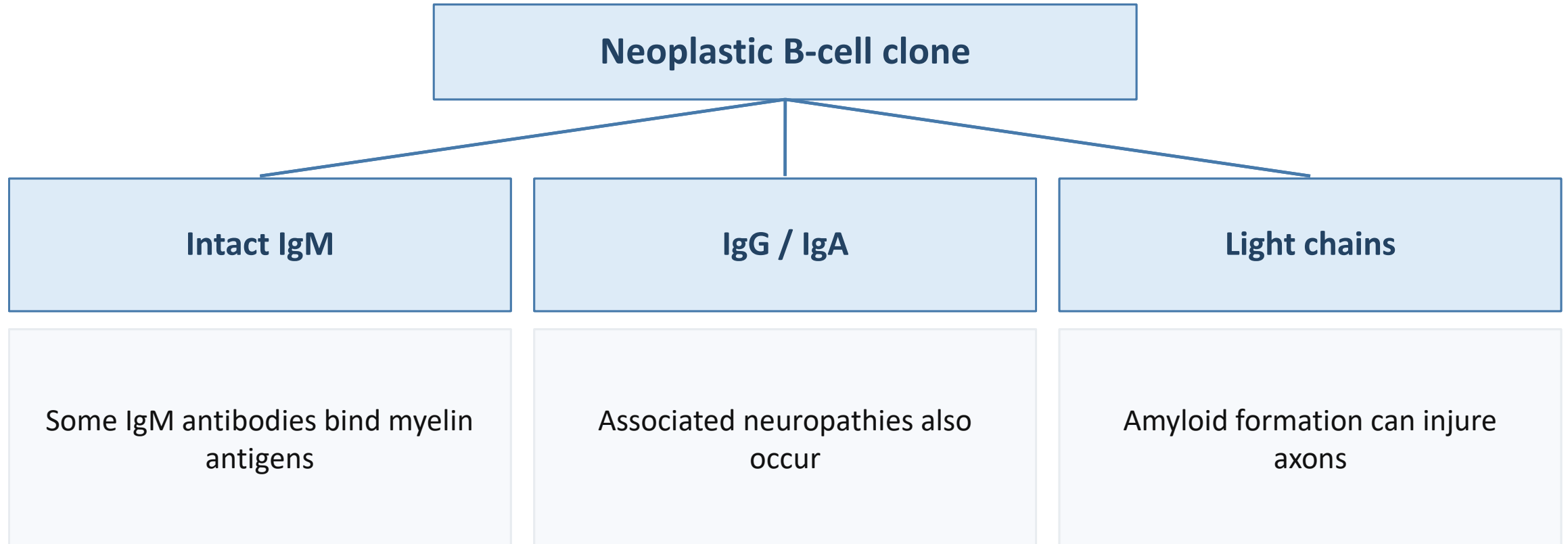
- Plexopathy may occur without direct tumor invasion.
- Autonomic neuropathy is also recognized.

What a paraneoplastic antibody can—and cannot—say

Separate disease association, antigen recognition, and tissue injury.

- An associated neuronal antibody can support a cancer-linked immune hypothesis.
- Anti-Hu detection alone does not show antibody-driven destruction of dorsal root ganglia.
- The neuropathy phenotype and temporal cancer relationship remain essential.

Monoclonal gammopathy: The causal chain

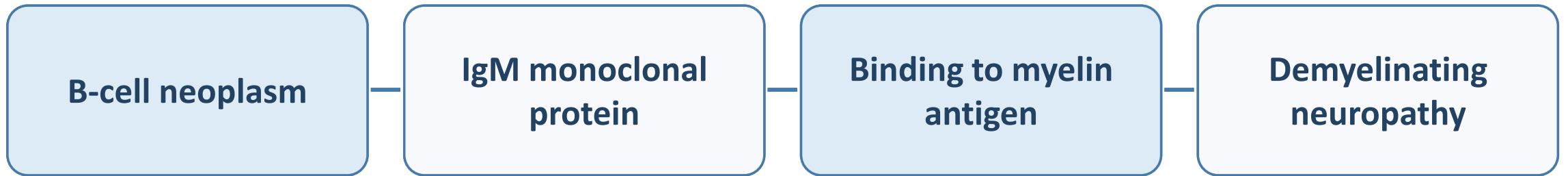


What is a paraprotein in this setting?

The tumor product, not necessarily the tumor mass, injures nerve.

- Neoplastic B cells can secrete monoclonal immunoglobulins or immunoglobulin fragments.
- These tumor-derived products are termed paraproteins.
- Nerve injury may follow antigen binding, deposition, amyloid effects, or multiple pathways.

IgM paraprotein: Myelin-directed injury



Robbins gives myelin-associated glycoprotein as a myelin antigen.

Myelin-associated glycoprotein as a target

IgM–myelin recognition links clone biology to myelin pathology.

- Some pathogenic IgM paraproteins are thought to bind myelin-associated antigens.
- Myelin-associated glycoprotein (MAG) is a specified example.
- Binding to a myelin antigen provides a mechanistic explanation for demyelinating disease.

IgM deposition: Myelin lamellae schematic

Schematic illustration — layer relationships only; Not electron microscopy



Myelin membranes / lamellae

Paraprotein deposition between layers

Interpreting a demyelinating IgM neuropathy

Electron-microscopic location: Between myelin membrane layers.

- The dominant lesion is associated with myelin rather than primary axonal dropout.
- IgM deposition can be seen between layers of the myelin sheath ultrastructurally.
- The textbook's observation is a morphologic association, not an image provided in this deck.

Other immunoglobulin classes

IgG OR IgA PARAPROTEINS

- IgG and IgA monoclonal proteins may also be associated with peripheral neuropathy.
- The textbook does not assign every such case one uniform mechanism.
- Do not assume the IgM–MAG model automatically applies to all classes.

POEMS: The named multisystem syndrome

POEMS syndrome

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graph TD; A[POEMS syndrome] --> B[P]; A --> C[O]; A --> D[E]; A --> E[M]; A --> F[S]; B --> G[Polyneuropathy]; C --> H[Organomegaly]; D --> I[Endocrinopathy]; E --> J["Monoclonal gammopathy"]; F --> K[Skin changes];
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P

Polyneuropathy

O

Organomegaly

E

Endocrinopathy

M

Monoclonal
gammopathy

S

Skin changes

POEMS neuropathy

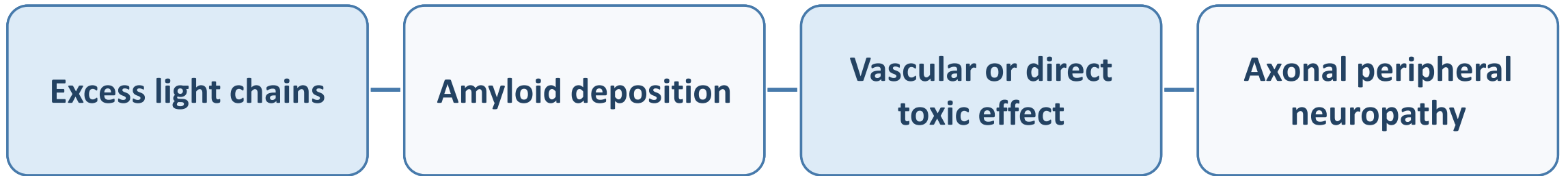
Distinctive pairing: Systemic features + demyelinating neuropathy.

- POEMS includes a demyelinating peripheral neuropathy.
- Paraprotein deposition occurs between noncompacted myelin lamellae.
- The neuropathy is part of a multisystem syndrome, not an isolated electrophysiologic label.

Two paraprotein–myelin associations

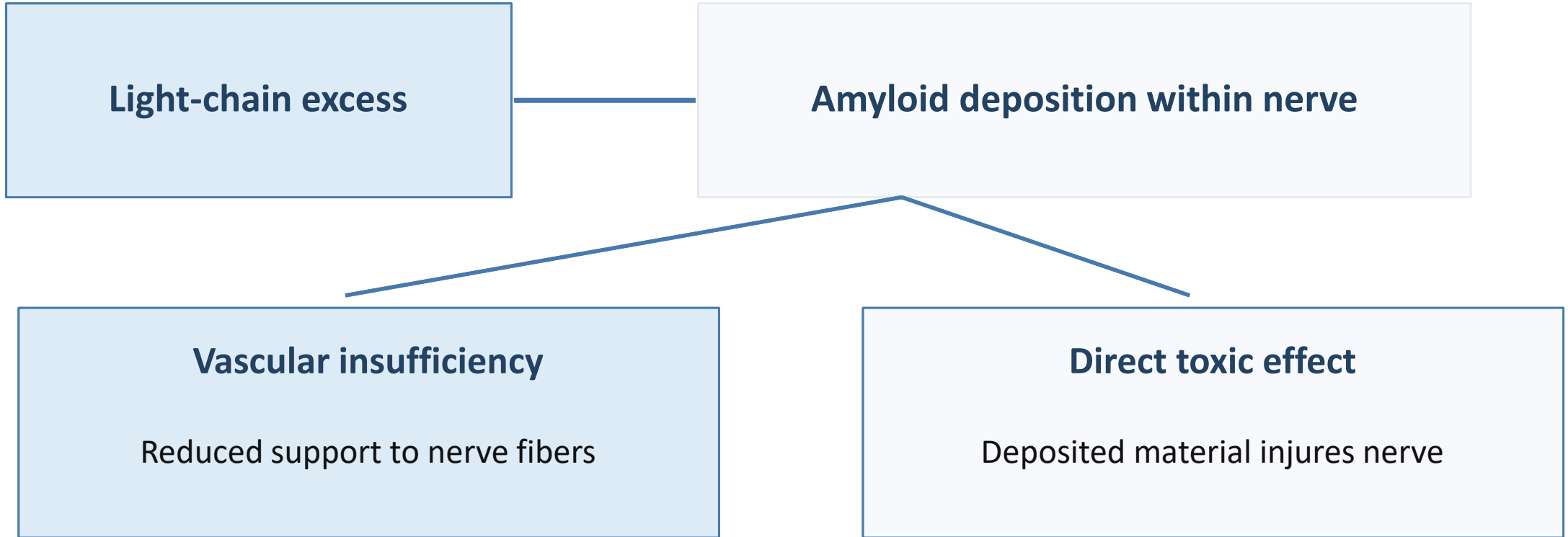
Feature	IgM / MAG model	POEMS description
Associated product	IgM paraprotein	Paraprotein in monoclonal gammopathy
Reported morphology	IgM between myelin membrane layers	Deposition between noncompacted lamellae
Clinical framing	Demyelinating peripheral neuropathy	Demyelinating neuropathy + multisystem features

Free light chains can create amyloid



This is a different downstream lesion from paraprotein-associated demyelination.

Light-chain amyloid: Two routes to nerve injury



Amyloid mechanism: Vascular insufficiency

AMYLOID
→
VASCULAR INSUFFICIENCY

- Deposited light-chain amyloid may impair the vascular support of peripheral nerve.
- Reduced vascular supply is one route to axonal injury.
- This does not establish that every amyloid neuropathy is exclusively ischemic.

Amyloid mechanism: Direct neurotoxicity

AMYLOID
→
DIRECT TOXIC EFFECT

- The textbook gives direct toxicity as another pathway to neuropathy.
- The ultimate peripheral-nerve injury is described as axonal.
- The vascular and toxic explanations are alternatives that may coexist.

Paraprotein neuropathies: Mechanism comparison

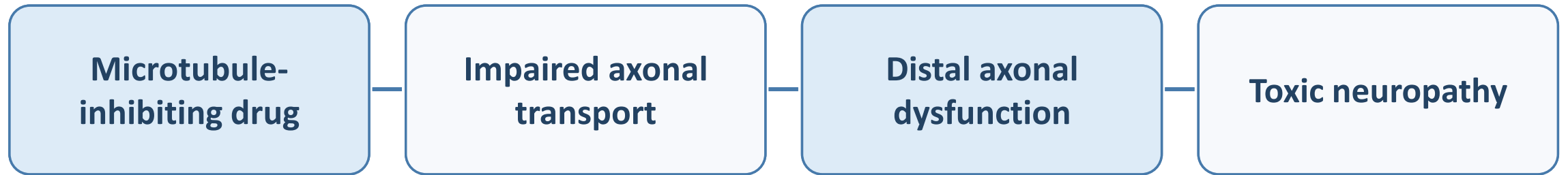
Product / syndrome	Proposed lesion	Typical pathology pattern
IgM paraprotein	Myelin antigen binding / deposition	Demyelinating neuropathy
POEMS	Deposition in noncompacted myelin	Demyelinating neuropathy
Light-chain amyloid	Vascular insufficiency or toxic injury	Axonal neuropathy

Treatment-related neuropathy is a separate category

Cancer association alone does not identify causation.

- Peripheral neuropathy can be a complication of anticancer treatment.
- Drug injury should be distinguished from tumor compression and paraneoplastic immune disease.
- Robbins specifically discusses cytotoxic chemotherapy and immune checkpoint inhibitors.

Vinca alkaloids and taxanes: Axonal transport

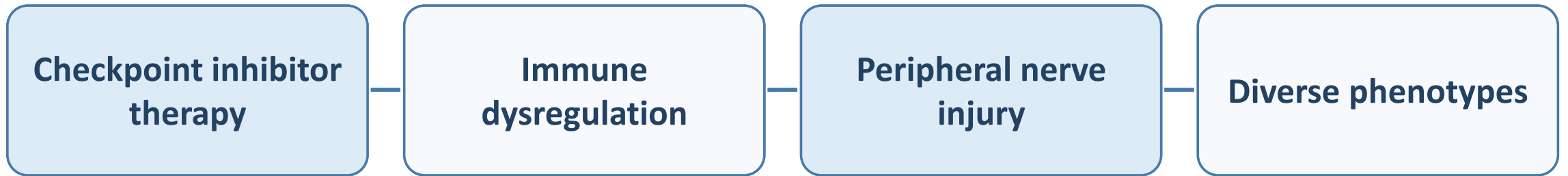


Interference with axonal transport is the mechanism emphasized by Robbins.

Platinum-related neuropathy

- Cisplatin is identified among chemotherapeutic causes of peripheral neuropathy.
- The parent section recognizes platinum compounds among potential sensory neuron–injuring toxins.
- Do not automatically attribute a neuropathy in a cancer patient to paraneoplastic immunity.

Immune checkpoint inhibitor–related injury



The clinical pattern is not restricted to a distal symmetric axonal neuropathy.

Checkpoint inhibitor neuropathy: Phenotypic range

Recognized pattern	Anatomic emphasis
Non-length-dependent polyradiculopathy	Root / nerve involvement, potentially proximal and distal
Axonal or demyelinating features	Different injury compartments can be affected
Cranial neuropathy	Cranial nerve localization
Sensory neuronopathy	Sensory neuronal cell-body pattern

Cancer-associated neuropathy: Integrating the mechanisms

Etiologic group	Distinctive clue	Typical injury logic
Direct local effect	Restricted nerve / plexus / root distribution	Compression or infiltration
Paraneoplastic	May precede tumor diagnosis; diverse immune phenotypes	Immune-related axonal / neuronal / myelin injury
Paraprotein-mediated	Monoclonal immunoglobulin or light chains	Myelin binding / deposition / amyloid
Treatment-related	Neuropathy arising in therapy context	Axonal transport toxicity or immune toxicity

Practical clinicopathologic reasoning

**Describe deficit
pattern**

**Localize affected
structure**

**Identify exposure /
protein / tumor**

**Select likely
mechanism**

A definitive attribution requires more than finding a malignancy alongside neuropathy.

Application I: Focal deficit and lung apex

HYPOTHETICAL TEACHING VIGNETTE

A patient is found to have an apical pulmonary neoplasm and a new focal upper-limb neurologic deficit. The deficit follows a plexus distribution.

Which malignancy-associated mechanism is most directly suggested?

Application I: Interpretation

Finding

Focal upper-limb findings localize to the brachial plexus.

Interpretation

Direct tumor-related brachial plexopathy is the leading mechanistic category.

Mechanistic rationale

Robbins explicitly associates tumors of the lung apex with brachial plexopathy.

Application II: Sensory syndrome before tumor recognition

HYPOTHETICAL TEACHING VIGNETTE

A patient develops distal sensory symptoms in an asymmetric, multifocal pattern. A cancer diagnosis has not yet been established.

Which paraneoplastic syndrome and cancer association should be considered?

Application II: Interpretation

Finding

Asymmetric, multifocal sensory onset suggests a sensory neuronopathy pattern.

Interpretation

A paraneoplastic sensory neuronopathy is a possible explanation; Small cell lung cancer is a major association.

Mechanistic rationale

Anti-Hu / ANNA-1 may be present; DRG damage appears to involve CD8⁺ cytotoxic T cells.

Application III: Monoclonal IgM and slow conduction

HYPOTHETICAL TEACHING VIGNETTE

A B-cell neoplasm produces a monoclonal IgM protein. Peripheral nerve conduction studies indicate a demyelinating process.

What antibody–target relationship fits the source description?

Application III: Interpretation

Finding

Demyelination identifies the myelin compartment as a major injury site.

Interpretation

The IgM paraprotein may bind myelin-associated glycoprotein or another myelin antigen.

Mechanistic rationale

IgM may accumulate between myelin membrane layers, as described ultrastructurally.

Application IV: Lymphoma without a prior systemic diagnosis

HYPOTHETICAL TEACHING VIGNETTE

A patient presents with peripheral nerve dysfunction. Tissue evaluation establishes infiltrating lymphoma cells within the involved nerve, although no systemic lymphoma was previously recognized.

What is the diagnosis and why is the timing plausible?

Application IV: Interpretation

Finding

Neoplastic cells infiltrate peripheral nerve tissue.

Interpretation

This defines neurolymphomatosis, most often associated with non-Hodgkin B-cell lymphoma.

Mechanistic rationale

Roughly half lack a known systemic lymphoma at diagnosis.

High-yield synthesis: Mechanism drives explanation

Cancer and peripheral-nerve injury

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graph TD; A[Cancer and peripheral-nerve injury] --> B[Direct]; A --> C[Immune]; A --> D[Protein]; A --> E[Iatrogenic]; B --> B1[Nerve, plexus or root infiltration / compression]; C --> C1[Paraneoplastic antibodies, T cells and diverse phenotypes]; D --> D1[IgM, POEMS and light-chain amyloid]; E --> E1[Cytotoxic drugs and checkpoint inhibitors];
```

Direct

Nerve, plexus or root
infiltration /
compression

Immune

Paraneoplastic
antibodies, T cells and
diverse phenotypes

Protein

IgM, POEMS and light-
chain amyloid

Iatrogenic

Cytotoxic drugs and
checkpoint inhibitors

Primary source and scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) · Chapter 27 · Peripheral Nerves and Skeletal Muscles

Primary topic: Neuropathies Associated With Malignancy (printed p. 1113)

Additional parent context: general nerve injury, anatomic patterns and toxic neuropathies (pp. 1106–1113)

Original diagrams and teaching vignettes; no textbook figures or patient specimens reproduced.