

Other Types of Nerve Sheath Tumors

Peripheral nerve sheath pathology

MMNST • Granular cell tumor • Perineurioma

Dr Abu Suraih Sakhri

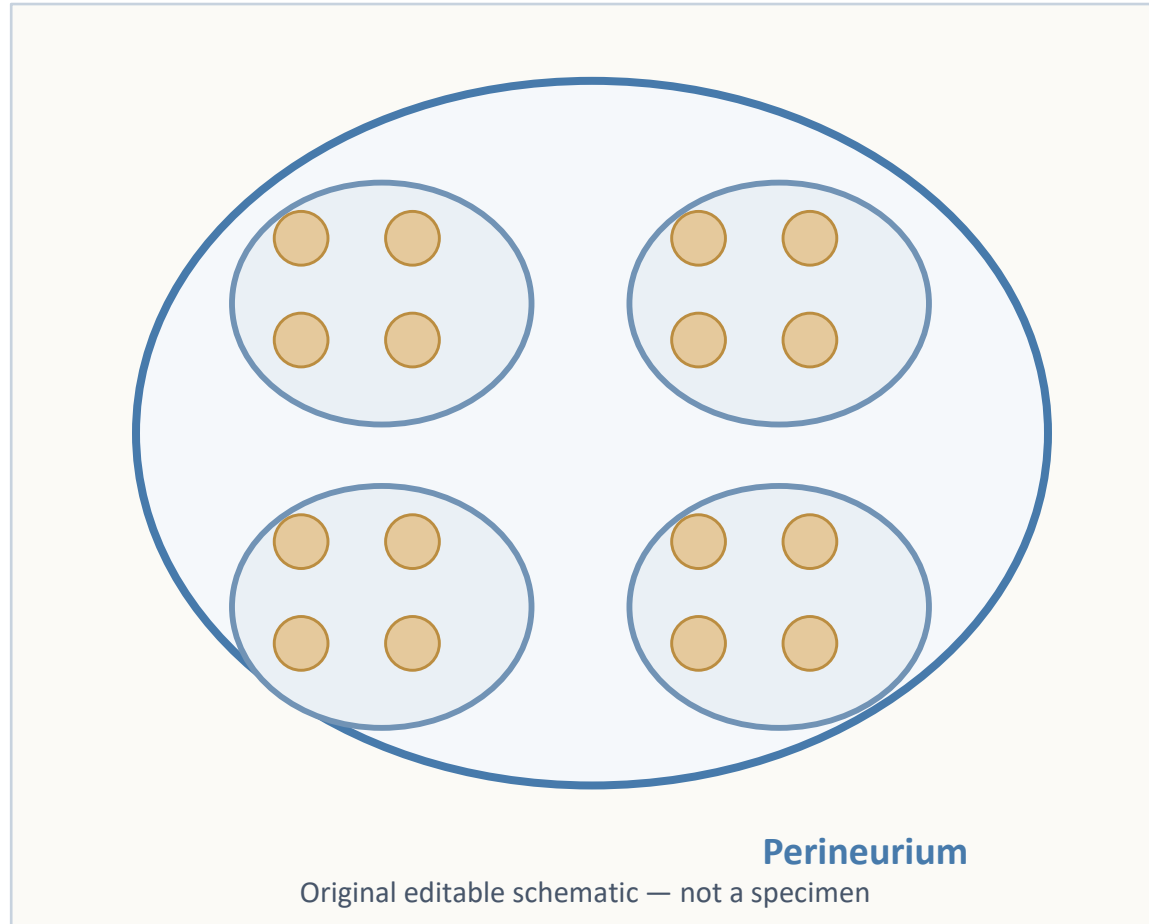
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Relate nerve-sheath anatomy to Schwann-cell and perineurial differentiation.
- Recognize the defining morphologic, immunophenotypic and molecular findings of three uncommon tumors.
- Resolve key diagnostic differentials using integrated pathology rather than a single stain.
- Link tumor identification to biologic behavior and potential syndromic evaluation.

Nerve sheath contains distinct cellular compartments



Schwann cells ensheath peripheral axons and form myelin around many axons.

Perineurial cells encircle nerve fascicles and contribute to the blood–nerve barrier.

Histologically different tumors can arise from these related peripheral nerve compartments.

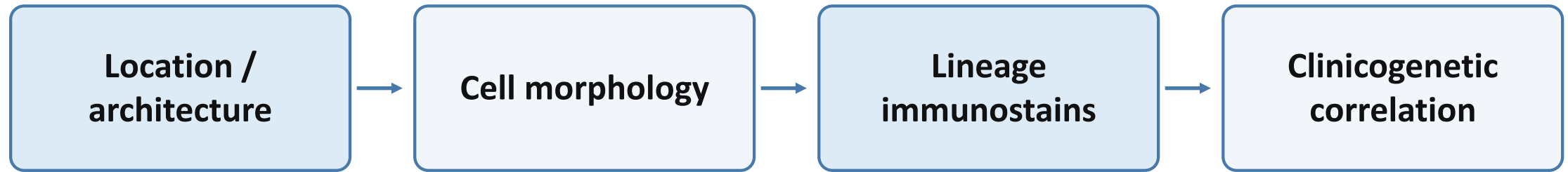
Three unusual tumors: Not one biologic group

Diagnostic feature	Malignant melanotic	Granular cell	Perineurioma
Lineage	Schwannian / melanocytic	Schwannian	Perineurial
Defining clue	Melanin $\pm$ psammoma bodies	Lysosomal granules	Perineurial architecture
Typical behavior	Aggressive potential	Usually benign	Benign

Conventional tumors supply the diagnostic baseline

- Schwannoma: Encapsulated, often Antoni A/B and Verocay bodies.
- Neurofibroma: Heterogeneous Schwannian and stromal cells; Unencapsulated.
- MPNST: Usually infiltrative, atypical spindle-cell sarcoma with variable Schwannian phenotype.
- A rare nerve-sheath tumor may be confused with any of these.

How to approach an unfamiliar nerve-associated mass



Start with anatomical compartment and growth pattern.

Schematic mechanism / diagnostic sequence — concept simplified for teaching

Morphology directs immunohistochemistry

Initial morphologic pattern

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graph TD; A[Initial morphologic pattern] --> B[Pigmented epithelioid or spindle lesion → Schwannian plus melanocytic markers.]; A --> C[Polygonal cells with granular eosinophilic cytoplasm → Schwannian and lysosomal stains.]; A --> D[Whorled spindle cells or concentric intraneural layers → perineurial marker panel.];
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Polygonal cells with granular eosinophilic cytoplasm → Schwannian and lysosomal stains.

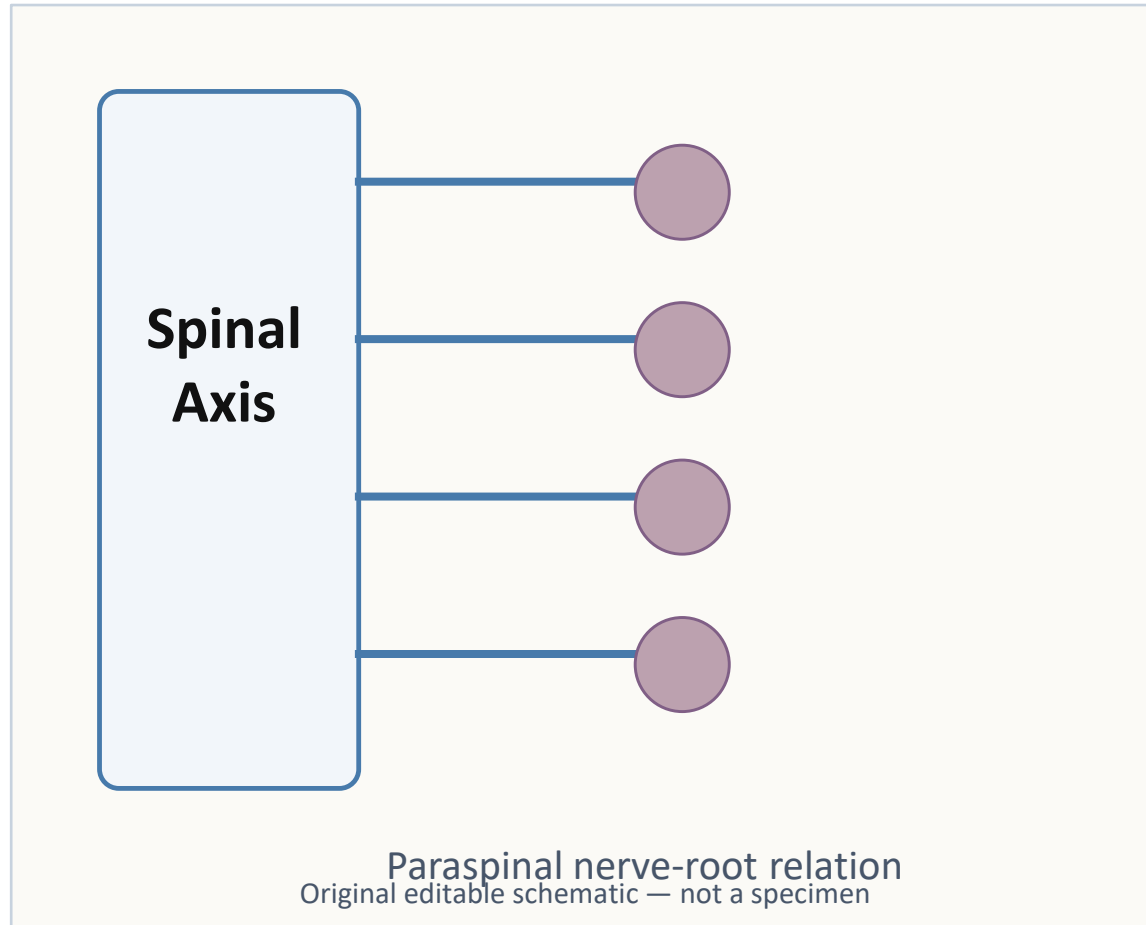
Whorled spindle cells or concentric intraneural layers → perineurial marker panel.

Schematic decision tree — interpret with site and histology

MMNST is separate from conventional schwannoma

- Former name: Melanotic schwannoma.
- Renamed to reflect malignant clinical behavior and distinct genetics.
- Key alteration: Inactivation of PRKAR1A; Not the typical NF2-driven schwannoma pathway.

Typical MMNST clinical setting

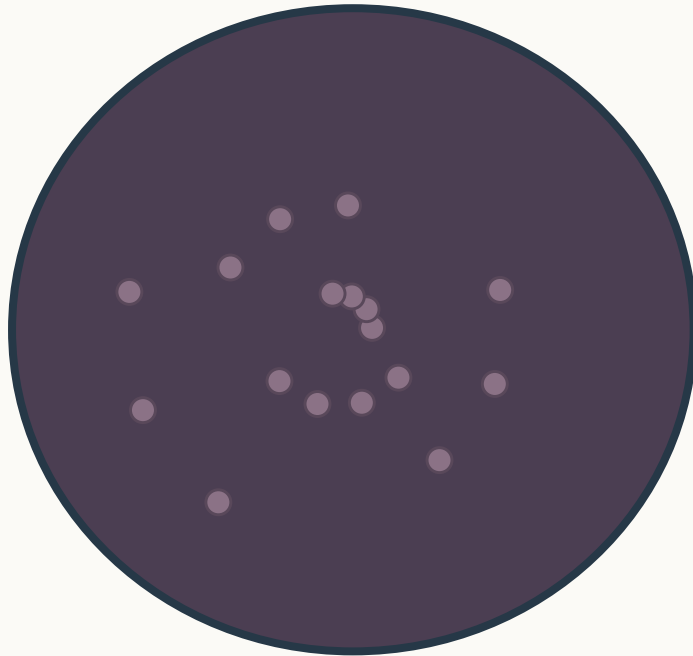


Often located near spinal nerve roots or autonomic nerves.

May present with a mass, pain, or neurologic compression symptoms.

Occurs sporadically or with Carney complex; Syndromic context must be assessed.

Gross appearance of MMNST



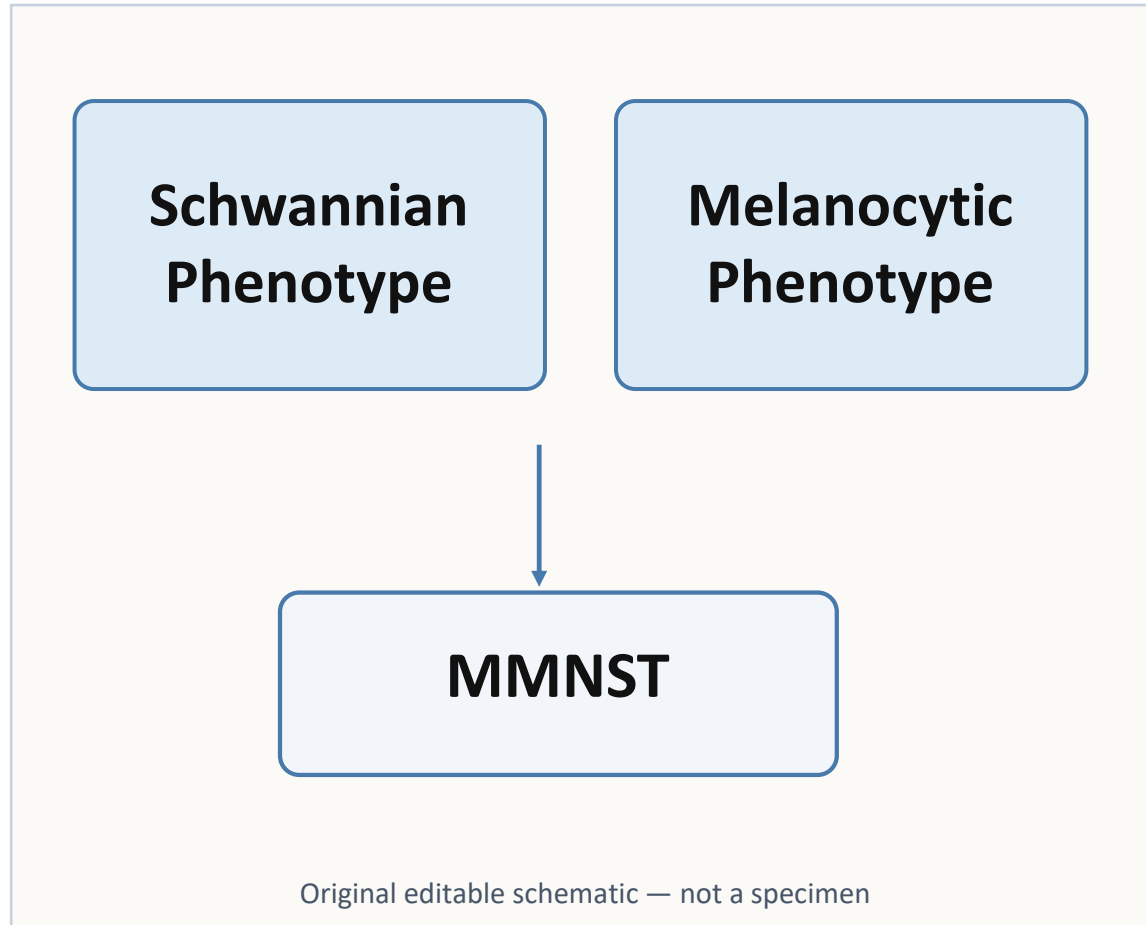
Original morphology schematic — not a histologic specimen

Typically a well-demarcated mass with conspicuous dark pigment.

Dark appearance results from intracytoplasmic melanin.

Macroscopic appearance alone cannot reliably establish its biological behavior.

MMNST shows dual differentiation

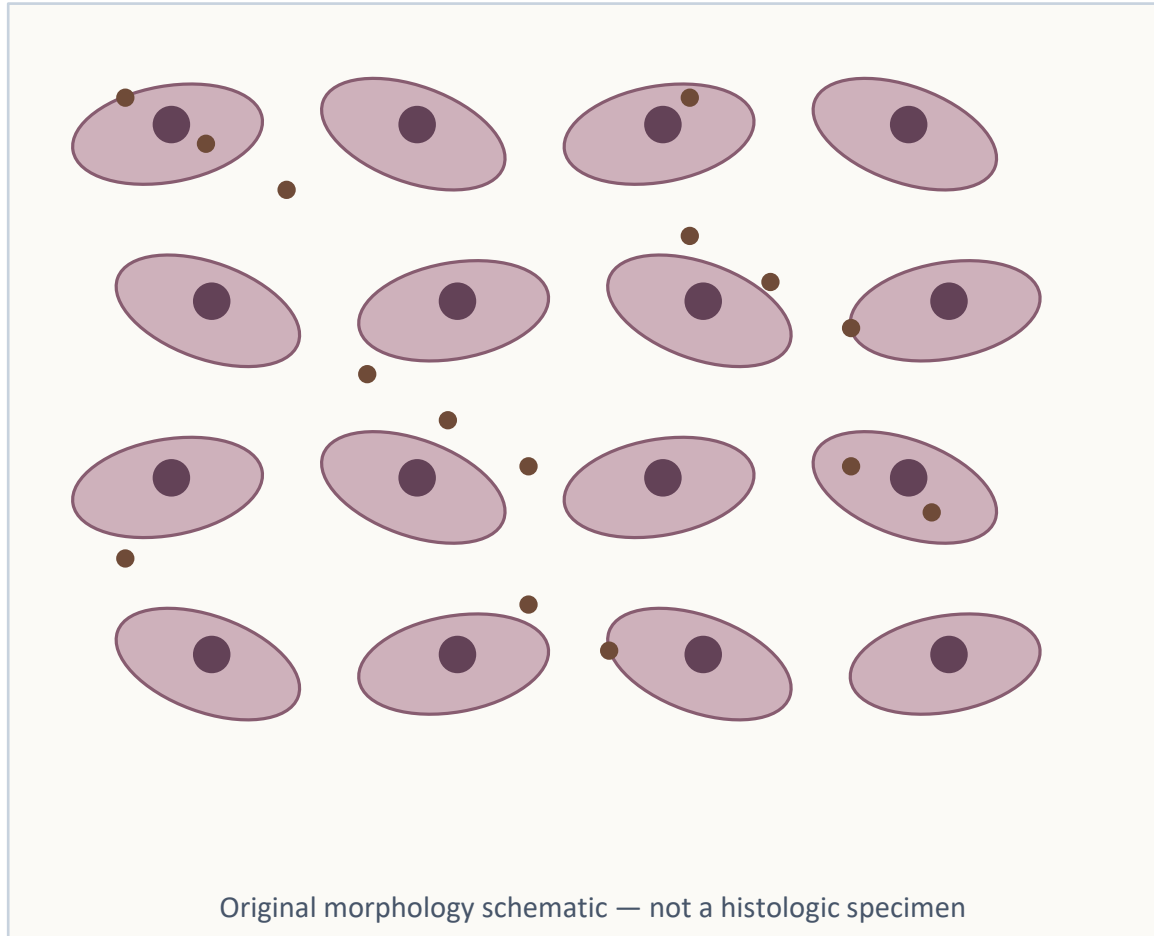


Schwannian features support nerve-sheath lineage.

Melanocytic differentiation explains melanin production and melanocytic marker expression.

Dual lineage is a diagnostic clue, not by itself proof against melanoma.

MMNST histologic architecture

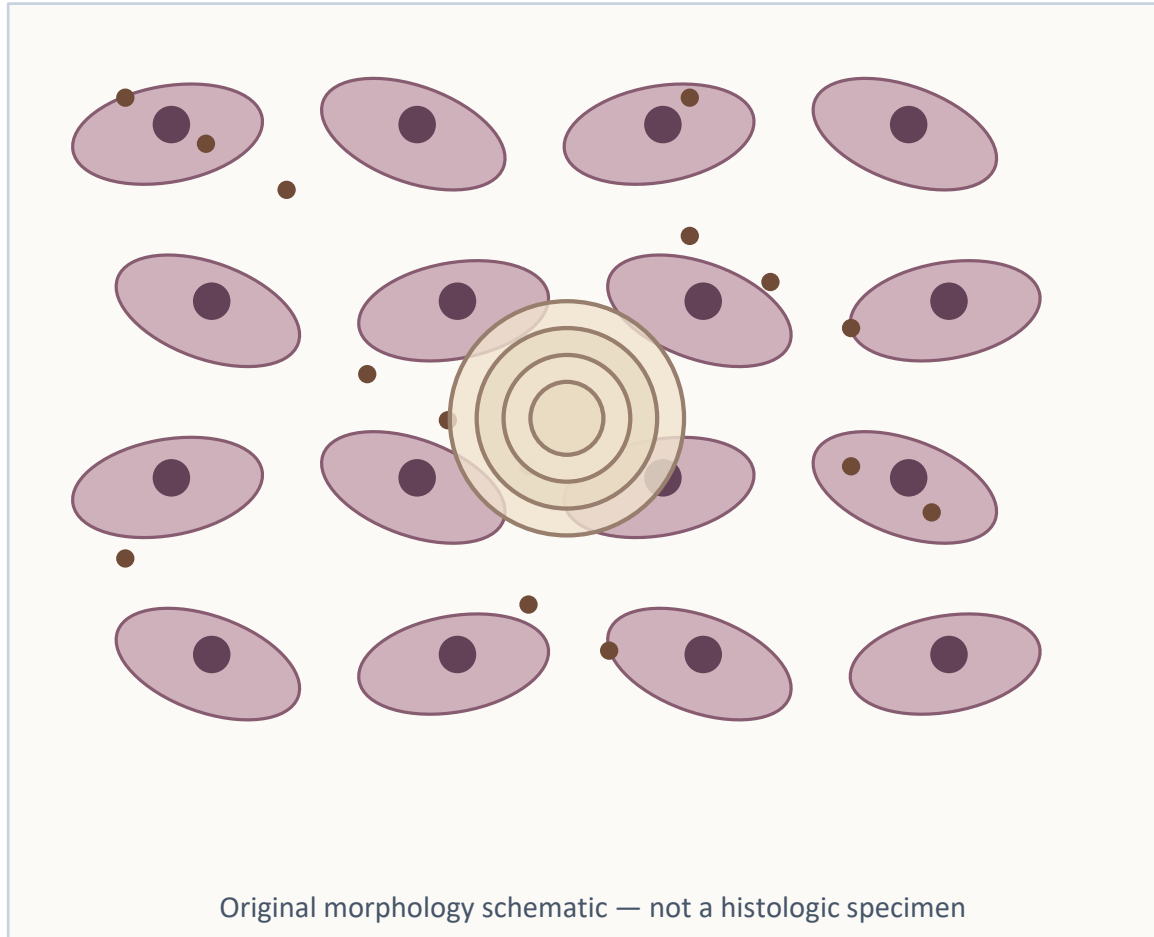


Plump spindle and epithelioid tumor cells may be arranged in nests, sheets, or short fascicles.

Cytoplasmic melanin ranges from focal to heavy pigmentation.

Nuclear grooves, intranuclear pseudoinclusions, or conspicuous nucleoli may occur.

Psammoma bodies are an important clue



Concentric lamellated calcifications may appear in MMNST.

Their presence supports a psammomatous phenotype, not a separate benign tumor.

Absence of psammoma bodies does not exclude MMNST.

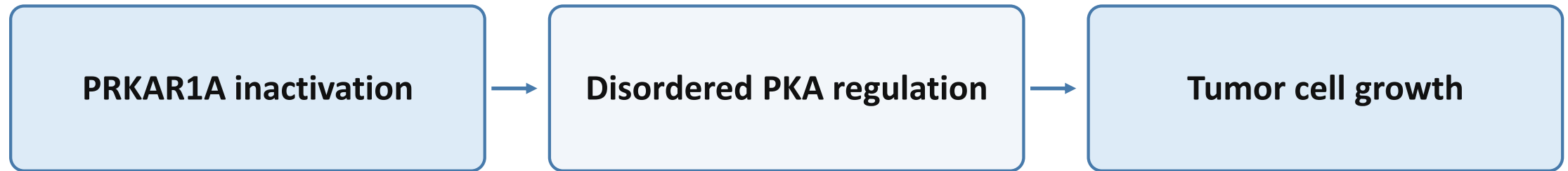
Psammomatous does not mean indolent

- Psammomatous lesions may be associated with Carney complex.
- Both psammomatous and nonpsammomatous tumors can behave aggressively.
- Do not use calcification to assign benign versus malignant potential.

MMNST immunophenotype: Two lineages

Diagnostic feature	Schwannian panel	Melanocytic panel
Examples	S100; SOX10	HMB45; Melan-A; tyrosinase
Interpretation	Neural-crest differentiation	Melanin synthesis pathway
Limitation	Also positive in melanoma	Also positive in melanoma

PRKAR1A is the molecular anchor



PRKAR1A encodes a regulatory subunit of cAMP-dependent protein kinase A.

Schematic mechanism / diagnostic sequence — concept simplified for teaching

PRKAR1A immunostaining has limitations

- Loss of PRKAR1A protein expression is supportive where present.
- Retained protein staining does not independently exclude MMNST.
- Interpret immunostaining alongside morphology, site, and molecular analysis.

Carney complex changes the clinical question

**Pigmented
Macules**

**Cardiac
Myxomas**

**Endocrine
Lesions**

Carney complex: Clinical features (not exhaustive)

Original editable schematic — not a specimen

Autosomal-dominant tumor-predisposition syndrome associated with PRKAR1A.

Includes spotty skin pigmentation, cardiac myxomas, and endocrine neoplasia.

An MMNST diagnosis may prompt focused clinical and genetic evaluation.

Syndromic association requires context

- Not every MMNST occurs in a patient with Carney complex.
- A psammomatous pattern is suggestive but not diagnostic of the syndrome.
- Personal and family history plus expert genetic assessment are more informative than a single morphologic feature.

MMNST should not be graded as a routine schwannoma

Diagnostic feature	Conventional schwannoma	MMNST
Behavior	Usually benign	Malignant potential
Molecular theme	NF2 inactivation common	PRKAR1A inactivation common
Management implication	Local control often curative	Long-term follow-up relevant

Histology alone may not predict MMNST outcome

- Low mitotic activity can coexist with later dissemination.
- Neither psammoma bodies nor absence of necrosis reliably establishes low risk.
- Avoid making definitive behavior predictions from one small sample.

Pigmented spindle-cell lesion: Differential diagnosis

- Metastatic melanoma: Frequently overlaps in S100, SOX10 and melanocytic stains.
- Pigmented epithelioid melanocytoma: Different clinicopathologic setting.
- Other pigmented neural-crest tumors and pigmented schwannoma-like lesions require integrated assessment.

MMNST versus melanoma: What contributes?

Evidence domain	Interpretation
Anatomy	Nerve-root relationship favors MMNST
Architecture	Psammoma bodies can support MMNST
IHC	Substantial overlap; not decisive alone
Genetics	PRKAR1A adds support; not infallible

MMNST diagnostic reporting: Preserve uncertainty

- Use the recognized entity name rather than “benign melanotic schwannoma.”
- Record the anatomic site and relationship to a nerve when established.
- Document relevant histologic features and limitations of sampling.
- Recommend multidisciplinary correlation for prognosis and syndromic features.

MMNST case: Anatomy and phenotype

Interpretive case / question

A pigmented paraspinal mass displays spindle/epithelioid cells and psammoma bodies.

Tumor cells are positive for SOX10 and HMB45.

Question: Why can these markers not completely exclude melanoma?

MMNST case: Unexpected low proliferation

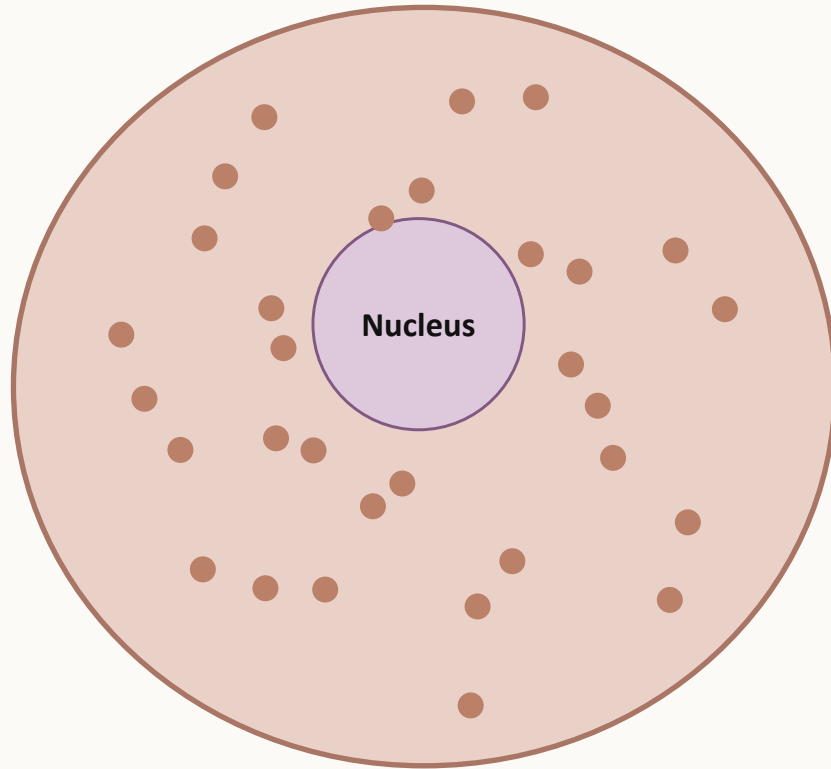
Interpretive case / question

A nerve-root mass has pigment, bland nuclei, and very few mitoses.

Question: Is “benign melanotic schwannoma” an appropriate final diagnosis?

No—low proliferative activity does not neutralize the entity’s metastatic potential.

Granular cell tumor: A lysosome-rich neoplasm



Original editable schematic — not a specimen

Typically a small superficial, subcutaneous, or mucosal mass.

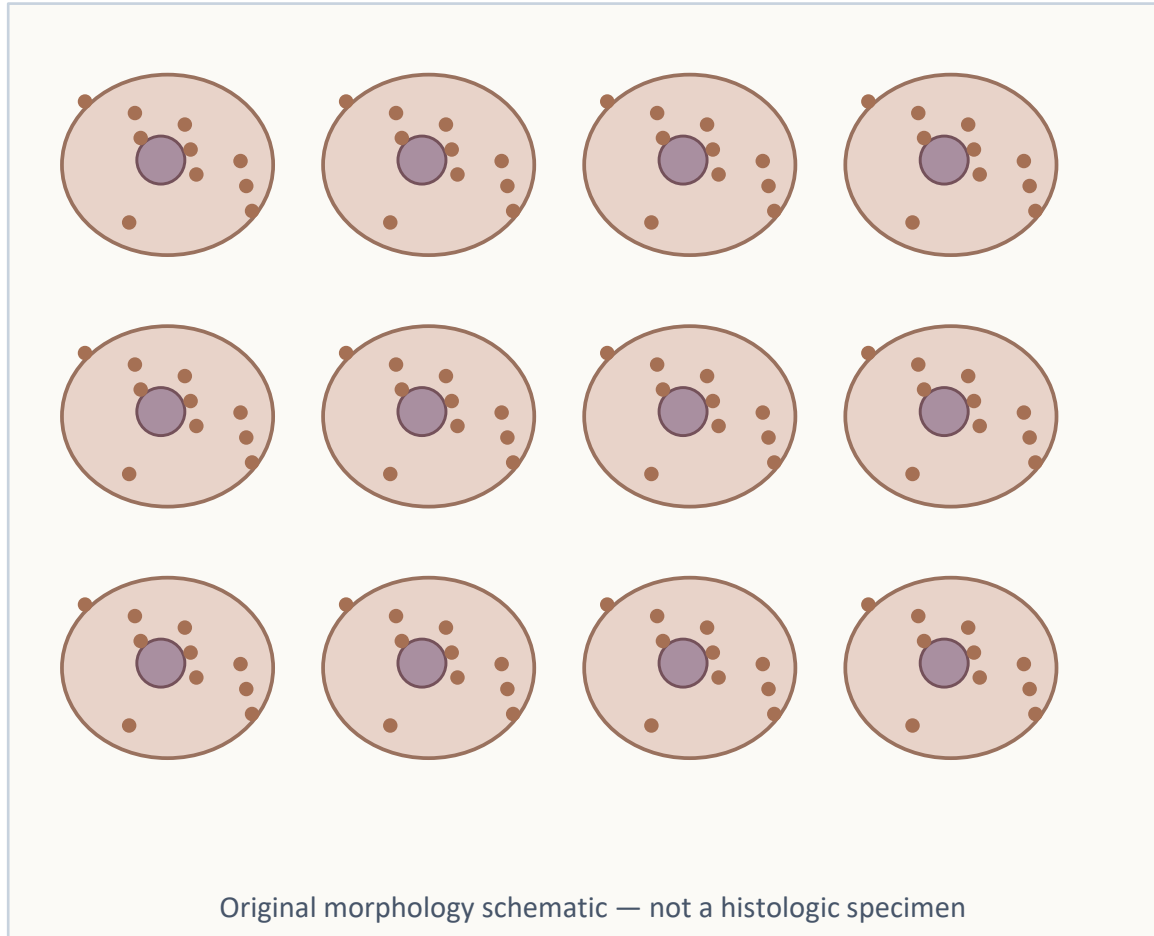
Most lesions are benign and show Schwannian differentiation.

Abundant intracytoplasmic lysosomes produce their characteristic granularity.

Common presentation of granular cell tumor

- May occur in the skin and mucosal surfaces, including the tongue.
- Usually presents as a slowly growing nodule rather than a neuropathy.
- Anatomic site may influence differential diagnosis and biopsy technique.

Granular cell tumor: Growth pattern

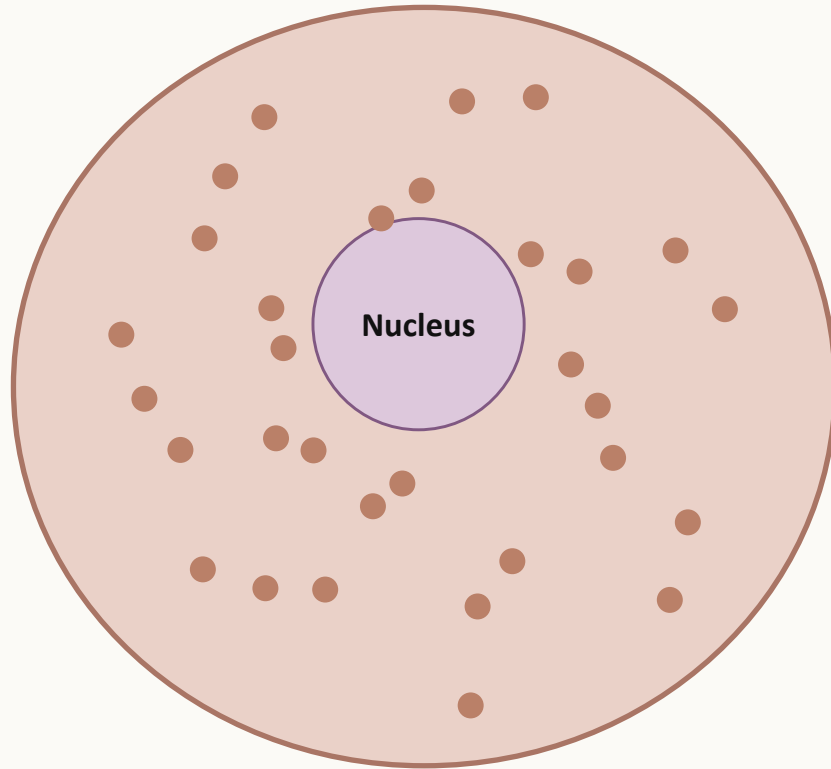


Usually unencapsulated; Nests and sheets may extend between native tissue structures.

This infiltrative-looking margin does not independently indicate malignancy.

Site-specific epithelial changes may complicate superficial biopsies.

Granular cytoplasm has a subcellular explanation



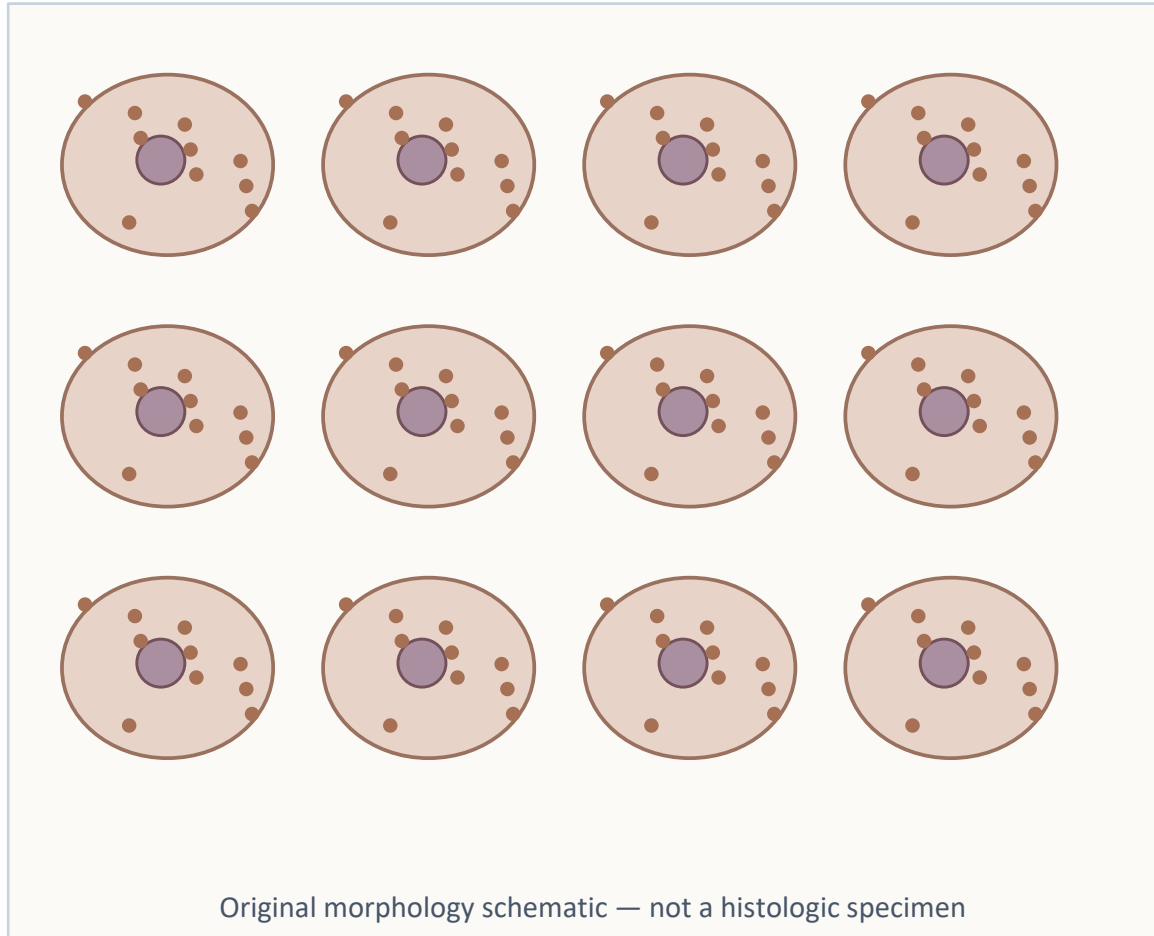
Original editable schematic — not a specimen

Tumor cells are plump or polygonal with abundant eosinophilic granular cytoplasm.

The granules correspond to lysosomes rather than melanin or mucin.

This observation leads to lysosome-related staining and molecular investigation.

Granular-cell nuclear features



Usually small, relatively uniform, centrally placed nuclei.

The cytoplasm commonly occupies much more of the cell than the nucleus.

Marked atypia, necrosis, or increased mitoses require additional assessment.

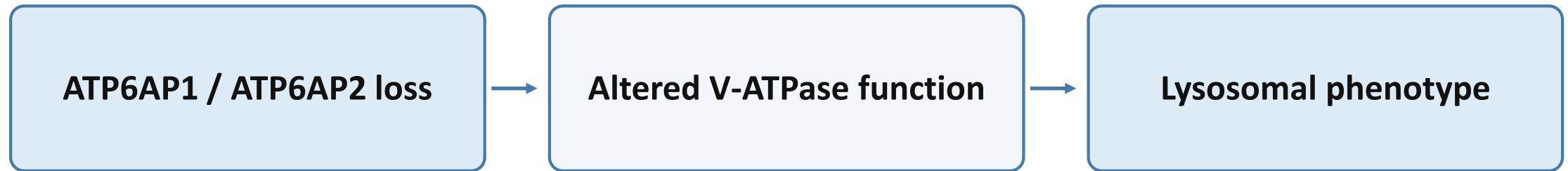
Granules can be highlighted histochemically

- Cytoplasmic granules often show PAS positivity with diastase resistance.
- PAS reflects the granular lysosomal contents—not a specific genetic event.
- Interpret special stains with H&E and immunohistochemistry.

Granular cell tumor: Practical immunopanel

Diagnostic feature	S100 / SOX10	CD68	Pan-cytokeratin
Typical role	Schwannian phenotype	Lysosome-associated staining	Epithelial exclusion
Caution	Not completely specific	Not evidence of histiocytic origin	Needs control/context

V-ATPase biology explains a key molecular link



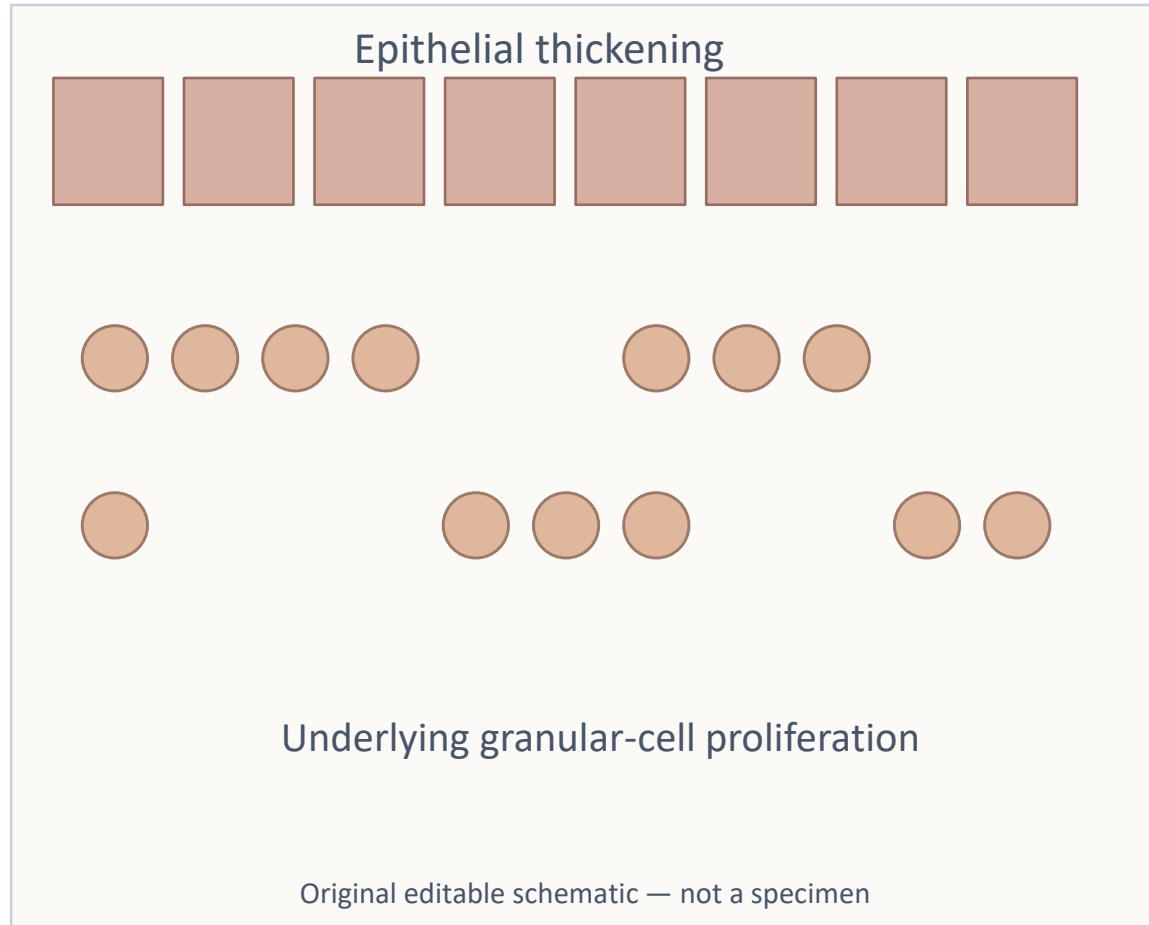
Genes ATP6AP1 and ATP6AP2 encode accessory components of the vacuolar H⁺-ATPase complex.

Schematic mechanism / diagnostic sequence — concept simplified for teaching

Granularity is a phenotype, not a diagnosis

- Numerous neoplasms and histiocytic lesions may contain granular cytoplasm.
- Confirm lineage and pattern rather than diagnosing on eosinophilic granules alone.
- Site, nuclear morphology, and immunophenotype remain decisive.

Superficial granular cell tumor can mimic SCC



Reactive pseudoepitheliomatous hyperplasia may overlie mucosal or cutaneous GCT.

In a shallow biopsy, the thickened squamous epithelium can dominate the section.

Look beneath epithelium for the underlying granular-cell neoplasm.

Pseudoepitheliomatous hyperplasia is not invasion

Diagnostic feature	Overlying reactive epithelium	Squamous carcinoma
Driver	Response to underlying GCT	Autonomous epithelial malignancy
Key question	Is there an underlying GCT?	Is there malignant epithelial invasion?
Pitfall	Overcall in superficial biopsy	Miss carcinoma in inadequate sample

When should granular cell tumor be considered atypical?

- Concerning findings include necrosis, spindling, prominent nucleoli, and high mitotic activity.
- High nuclear-to-cytoplasmic ratio and significant pleomorphism are also assessed.
- These features should be interpreted systematically, not individually.

Fanburg-Smith criteria: Historical framework

Diagnostic feature	Architecture / injury	Nuclear / proliferation
Features	Spindling; necrosis	Prominent nucleoli; increased mitoses
Additional		High N:C ratio; pleomorphism

Granular cell tumor: Behavior is usually benign

- Most lesions remain localized after adequate removal.
- Rare malignant examples show recurrence or metastasis.
- The word “granular” itself makes no assertion of benign or malignant behavior.

Granular cell tumor versus other granular lesions

Initial morphologic pattern

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graph TD; A[Initial morphologic pattern] --> B[Histiocytic lesions may be CD68 positive but lack typical diffuse Schwannian phenotype.]; A --> C[Granular variants of non-neural tumors retain their original lineage markers.]; A --> D[A broad panel is preferable when morphology is atypical or site is unusual.];
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Histiocytic lesions may be CD68 positive but lack typical diffuse Schwannian phenotype.

Granular variants of non-neural tumors retain their original lineage markers.

A broad panel is preferable when morphology is atypical or site is unusual.

Schematic decision tree — interpret with site and histology

Granular cell tumor case: Tongue biopsy

Interpretive case / question

A tongue nodule contains sheets of bland polygonal cells with abundant granular cytoplasm.

An overlying squamous proliferation extends into the lamina propria.

Question: Which two components must be interpreted independently?

Granular cell tumor case: CD68 positivity

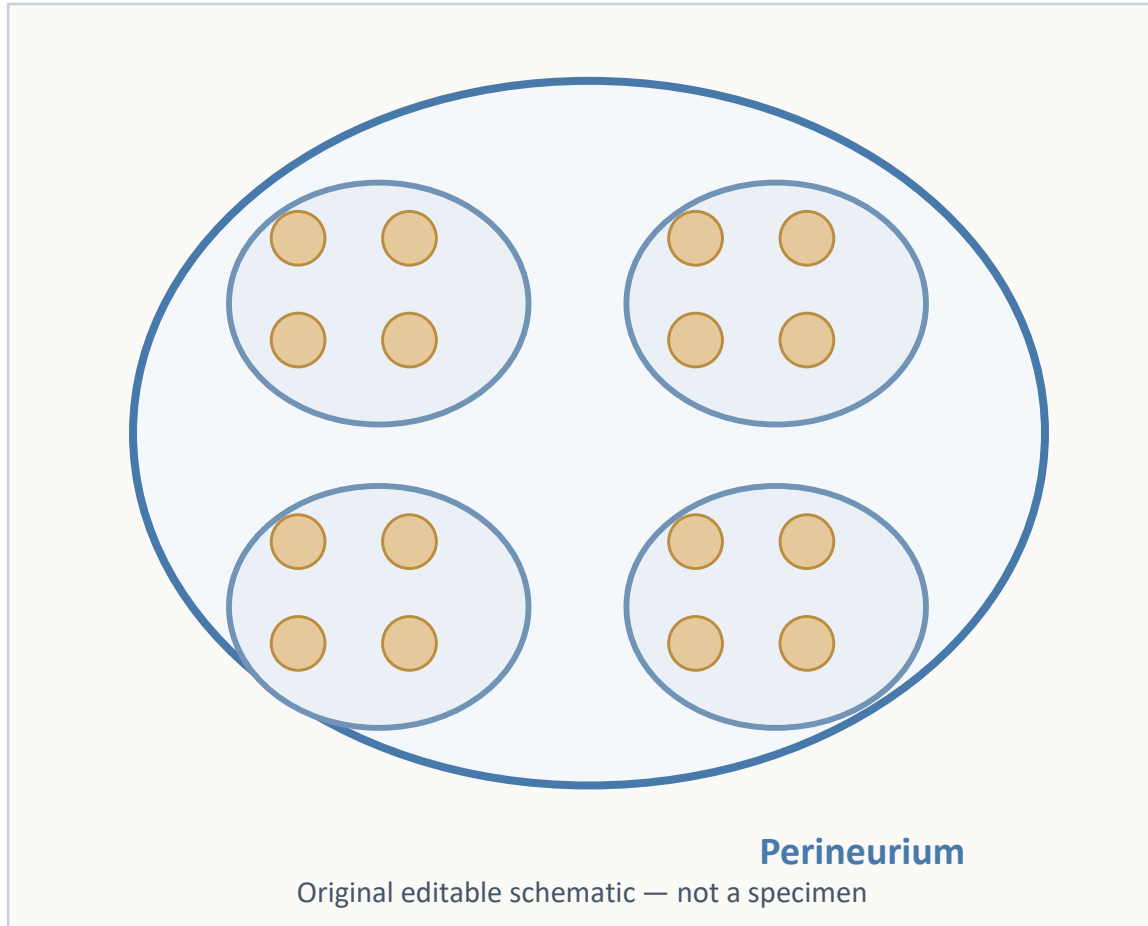
Interpretive case / question

A bland granular-cell neoplasm is S100 positive and CD68 positive.

Question: Does CD68 establish histiocytic lineage?

No. Granular lysosomes can produce CD68 positivity in Schwannian granular cell tumors.

Perineurioma originates in a different sheath layer



Perineurial cells normally surround nerve fascicles.

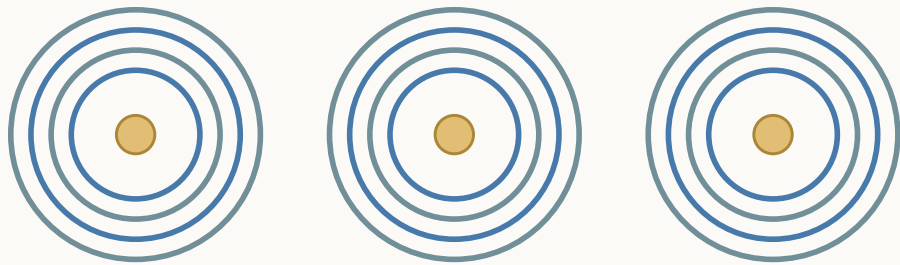
Perineurioma demonstrates perineurial rather than predominantly Schwann-cell differentiation.

Classic perineuriomas are benign lesions.

Two principal anatomic forms of perineurioma

Diagnostic feature	Intraneural	Soft tissue
Location	Within involved nerve	Outside major nerve
Pattern	Pseudo-onion bulbs	Storiform / whorled spindle cells
Presentation	Progressive neuropathic deficit	Localized soft tissue mass

Intraneural perineurioma: Lesion centered on fascicles



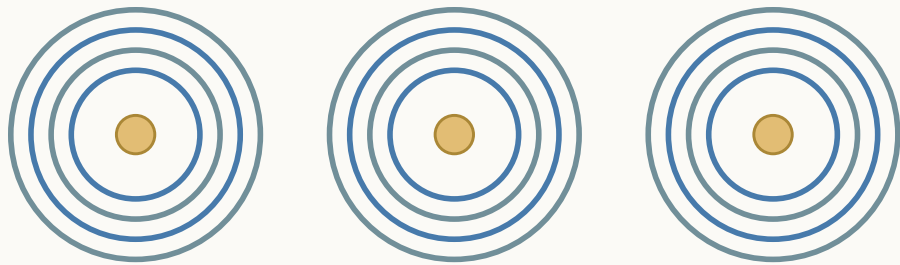
Original morphology schematic — not a histologic specimen

Typically presents as fusiform or segmental enlargement of a nerve.

Neoplastic perineurial cells are arranged around intraneural fibers.

Affected patients may develop slowly progressive motor or sensory impairment.

The pseudo-onion-bulb architecture



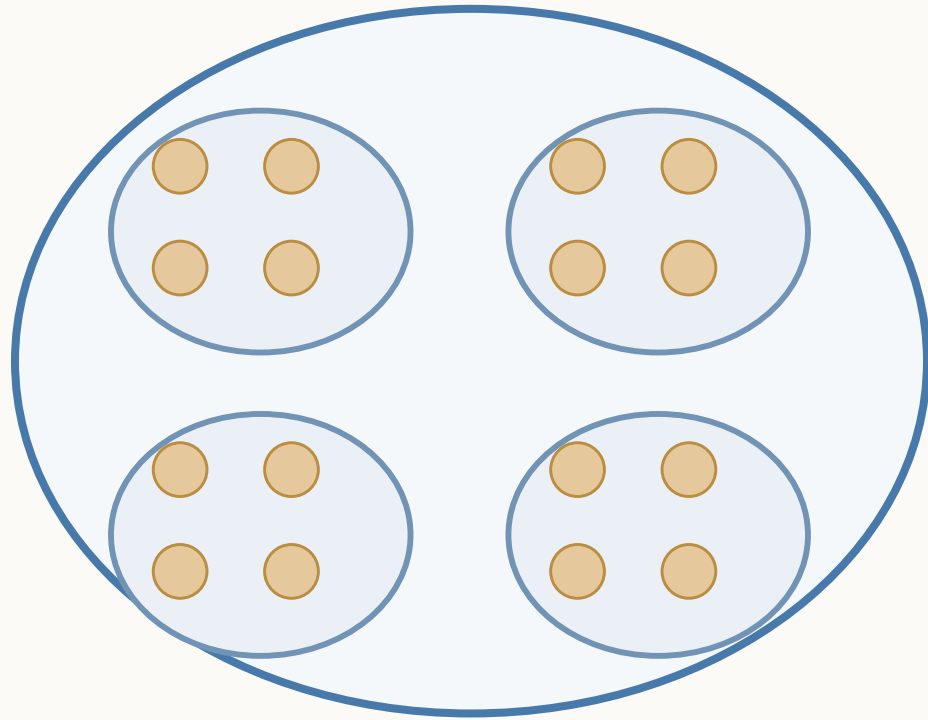
Original morphology schematic — not a histologic specimen

Concentric perineurial-cell processes wrap a central axon-associated compartment.

These layered structures are a hallmark of intraneural perineurioma.

True reactive onion bulbs in chronic neuropathies have different cellular origins.

Central axons help establish intraneural disease



Perineurium

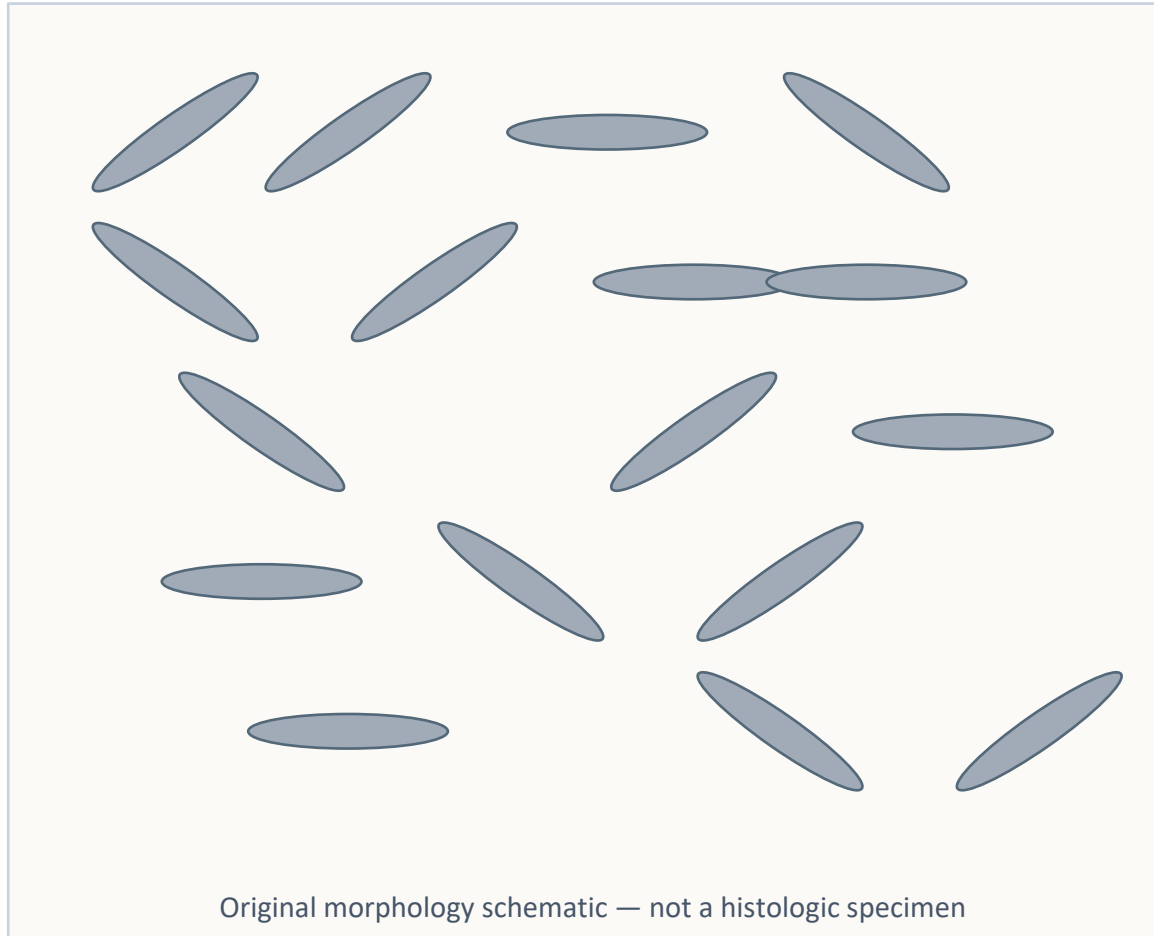
Original editable schematic — not a specimen

Neurofilament immunostaining can highlight residual central axons.

S100 labels associated Schwann cells but not the predominant perineurial tumor cells.

An axon-centered pattern helps distinguish intraneural from extraneural masses.

Soft-tissue perineurioma: Cell shape and pattern

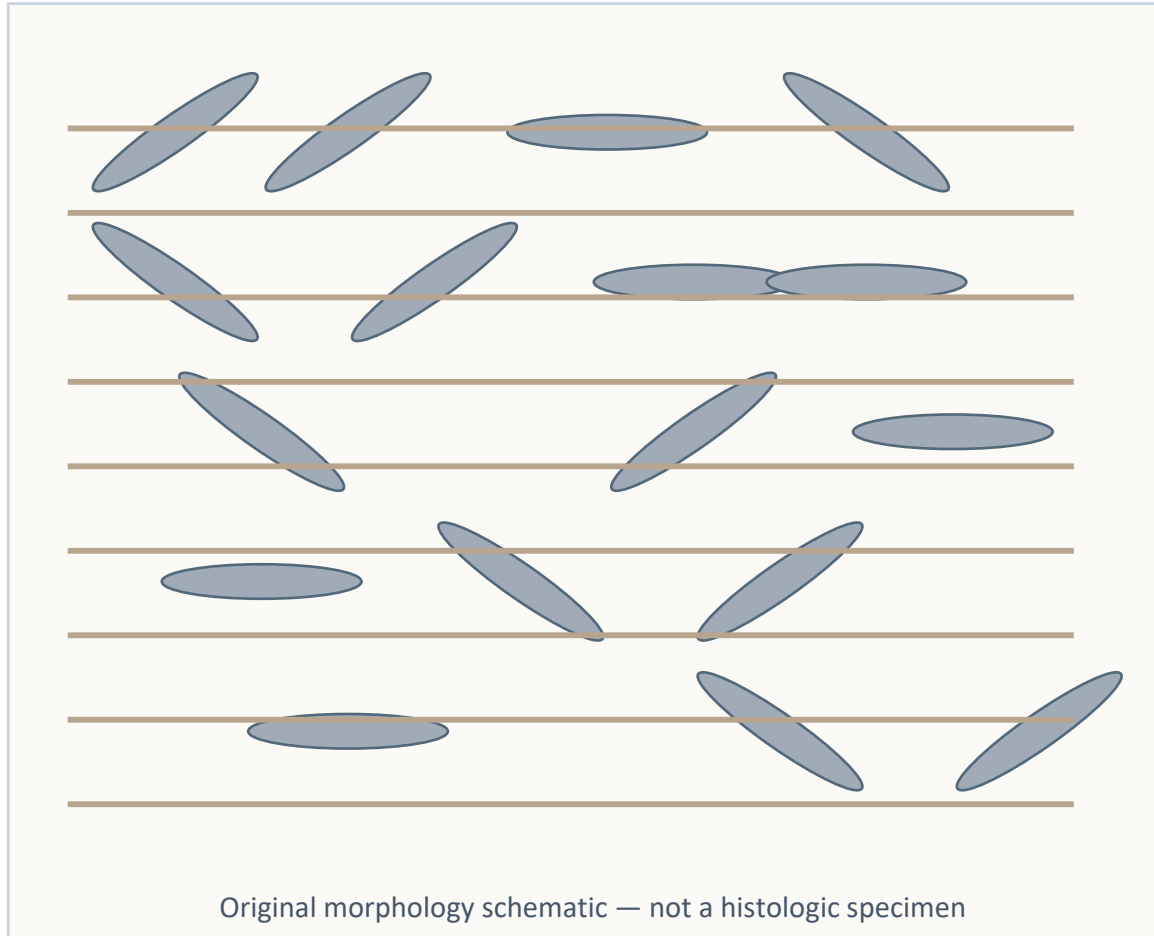


Bland spindle cells with long delicate bipolar processes.

Whorled, storiform, reticular, or fascicular growth in variable collagenous/myxoid stroma.

Usually a localized soft-tissue lesion with relatively limited atypia.

Sclerosing perineurioma emphasizes matrix



A subset has conspicuous collagen deposition and lower cellularity.

Dense sclerotic stroma can obscure delicate neoplastic cell processes.

Site, bland morphology, and perineurial stains are diagnostic anchors.

Perineurial IHC is a panel interpretation

Diagnostic feature	Perineurial cell markers	Schwann-cell markers
Typical pattern	EMA; claudin-1; GLUT1	S100; SOX10
Perineurioma	Often positive	Usually negative in tumor cells
Interpretive caution	Also present in native perineurium	Resident Schwann cells may be positive

Why EMA positivity alone is insufficient

- EMA can stain nonneoplastic perineurium around other nerve tumors.
- Other spindle-cell neoplasms may express EMA.
- The correct question is whether the tumor cells have the expected pattern and architecture.

Perineurioma molecular findings depend on location

Diagnostic feature	Intraneural	Soft tissue
Reported genetics	TRAF7, occasionally NF2	NF2/22q alterations and others
Biology	Benign perineurial proliferation	Benign perineurial proliferation
Main diagnostic tool	Architecture + IHC	Morphology + IHC

Perineurioma is not a demyelinating onion-bulb neuropathy

Diagnostic feature	Intraneural perineurioma	Reactive onion-bulb neuropathy
Cell population	Perineurial neoplastic layers	Schwann cell / reactive layers
EMA	Layers often positive	Does not mimic a full perineurial tumor pattern
Clinical context	Focal nerve enlargement	Diffuse / multifocal neuropathy context

Soft-tissue perineurioma versus neurofibroma

Diagnostic feature	Perineurioma	Neurofibroma
Predominant lineage	Perineurial	Schwannian plus stromal cells
EMA	Tumor cells often positive	Often highlights admixed perineurial cells
S100/SOX10	Tumor cells largely negative	Schwannian tumor subset positive

Perineurioma versus low-grade fibromyxoid sarcoma

- Both may show bland spindle cells and myxoid/collagenous areas.
- MUC4 expression or relevant gene fusion can support low-grade fibromyxoid sarcoma in a difficult case.
- EMA alone may not resolve the differential.

Perineurioma reporting should prioritize anatomy

- Specify intraneural versus soft-tissue localization when established.
- Describe the perineurial growth pattern and the tumor-cell immunophenotype.
- Correlate neural involvement with functional deficits and surgical planning.

Intraneural perineurioma case: Progressive weakness

Interpretive case / question

A young patient has slowly progressive focal weakness and segmental nerve enlargement.

Biopsy reveals axon-centered concentric cellular layers.

Question: Which stains best assign the layers and central axons?

Soft-tissue perineurioma case: Bland spindle mass

Interpretive case / question

A superficial mass contains slender spindle cells in a whorled fibromyxoid pattern.

Tumor cells show EMA and claudin-1, with little/no SOX10 in lesional cells.

Question: Which cell lineage is supported?

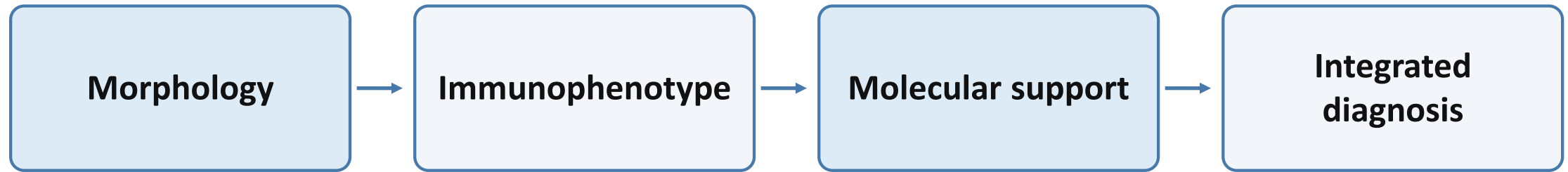
Three tumors: A high-yield integrated comparison

Diagnostic feature	MMNST	Granular cell tumor	Perineurioma
Cytoplasm	Melanin	Lysosomal granules	Slender processes
Main markers	S100 / SOX10 + HMB45	S100 / SOX10; CD68	EMA / claudin-1 / GLUT1
Molecular clue	PRKAR1A	ATP6AP1 / ATP6AP2	TRAF7 or NF2
Behavior	Aggressive potential	Mostly benign	Benign

Use stains to answer a morphologic question

- S100/SOX10: Support Schwannian lineage but not a unique diagnosis.
- HMB45/Melan-A: Establish melanocytic phenotype, not necessarily melanoma.
- CD68: May reflect lysosomes rather than macrophage lineage.
- EMA/claudin-1/GLUT1: Assess perineurial tumor cells, not just capsule.

Molecular findings are supportive—not solitary diagnoses



PRKAR1A points toward MMNST in the right clinicopathologic context.

Schematic mechanism / diagnostic sequence — concept simplified for teaching

Three distinct diagnostic hazards

Tumor	Pitfall	Corrective strategy
MMNST	False reassurance	Recognize aggressive entity
Granular cell	Squamous mimic	Inspect underlying GCT
Perineurioma	Lineage confusion	Cell-specific marker panel

Integrated practice vignette: Choose the diagnosis

Finding cluster	Leading consideration
Pigment + nerve root + dual markers	MMNST
Mucosal nodule + cytoplasmic granules	Granular cell tumor
Nerve enlargement + pseudo-onion bulbs	Intraneural perineurioma

Essential messages

- The microscopic compartment and phenotype dictate the diagnostic workup.
- MMNST differs fundamentally from benign conventional schwannoma.
- Lysosomal granularity and perineurial layering are distinctive clues—not standalone diagnoses.
- Integrated evaluation prevents both underestimation of malignancy and overtreatment of benign lesions.

Selected references

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