Pediatric peripheral nerve sheath tumors: pathology and associated syndromes

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Introduction

Pediatric peripheral nerve sheath tumors (PNST) are generally classified as soft tissue tumors but differ significantly from most other neoplasms in this category, presenting unique challenges in both classification and prognostication. Their exceptional nature is reflected in the fact that although currently discussed in the WHO Classification of Tumours of Soft Tissue (2013), they were not even included in the 2002 WHO publication. Notable differences between PNST’s and other soft tissue tumors include their frequent association with genetic disorders and the origin of a majority of malignant nerve sheath tumors from neurofibroma, a benign and common precursor lesion. Furthermore, these tumors are histologically diverse, arising in a complex tissue with distinctive anatomic compartments, including Schwann cells, the endoneurium, the perineurium and the epineurium. Vascular elements, fibroblasts and macrophages are also present in all three layers. Although theoretically neoplasms may arise from fibroblasts, perineural cells and other cells of the nerve sheaths, most are in fact derived from Schwann cells. These are neuroectodermal cells of neural crest origin unique to peripheral nerves, and the histologic diversity so characteristic of peripheral nerve tumors is in large part attributable to a metaplastic repertoire remarkable for its capacity for divergent differentiation.

As with other soft tissue neoplasms, the diagnosis and proper classification of peripheral nerve sheath lesions require correlation with clinical and surgical data as well as attention to their histologic and immunohistochemical features. This may be challenging when tissue is limited and other soft tissue lesions are in the differential diagnosis. However, an additional major challenge, particularly germane to the pediatric pathologist is the propensity of these tumors to arise in syndromic settings, such as neurofibromatosis 1, neurofibromatosis 2, multiple endocrine neoplasia, type 2b (MEN, 2b) and schwannomatosis predisposition syndrome. In childhood, tumor development may precede recognition of a syndrome, and it is often the pediatric pathologist who can make this clinically crucial connection. With modern molecular genetic techniques, our knowledge of these syndromes has advanced rapidly, and the pediatric pathologist can contribute, not just by establishing a correct tissue diagnosis, but also to suggest the need for additional testing. In terms of proper tissue diagnosis, a major challenge is to assess atypical or cellular variants (especially neurofibroma) and recognize transformation to a low grade malignant peripheral nerve sheath tumor. Although diagnosis of these
tumors at both the frankly benign and malignant ends of the spectrum is usually straightforward, it is a rare pediatric pathologist who has not faced the challenge of how to approach the diagnosis of an “atypical” tumor, and to communicate those findings to clinicians.

**Anatomy and histology**

The peripheral nervous system (PNS) comprises:

1) The 10 lower cranial nerves (III-XII)
2) Nerve roots of the spinal cord (SC)
3) Spinal ganglia, plexuses, nerve trunks and their terminations in the skin and muscles
4) Autonomic ganglia and nerves

The normal structure of peripheral nerve is illustrated below
The normal peripheral nerve consists of a bundle of fascicles encased in a fibrovascular stroma termed the EPINEURUM.

Individual peripheral and autonomic nerve fascicles are further ensheathed by PERINEURUM, a specialized structure functionally akin to the arachnoid membrane. Contained within the perineurium is the ENDONEURUM, consisting of a collagenous matrix housing the axons, Schwann cells, fibroblasts, macrophages, mast cells and capillaries. The axons are: myelinated and unmyelinated. Schwann cells are competent to produce myelin.
Histologic techniques for peripheral nerves

<table>
<thead>
<tr>
<th>Stains for immunochemistry</th>
<th>Purpose</th>
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<tbody>
<tr>
<td>Myelin Basic protein/Luxol fast blue</td>
<td>Myelin</td>
</tr>
<tr>
<td>S-100</td>
<td>Schwann cells, normal and neoplastic</td>
</tr>
<tr>
<td>Leu-7 (CD57)</td>
<td>Schwann cells, normal and neoplastic</td>
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<tr>
<td>Epithelial membrane antigen (EMA)</td>
<td>Perineural cells</td>
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<tr>
<td>Claudin-1</td>
<td>Perineural cells</td>
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<td>GLUT-1</td>
<td>Perineural cells</td>
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General Overview of peripheral nerve tumors and neurofibromatosis

Peripheral nerve sheath tumors encompass a spectrum of benign tumors, malignant tumors and tumors of intermediate biologic potential. In addition, there are several distinctive types of hamartomas and heterotopias that involve peripheral nerves, as well as difficult to classify subsets of peripheral nerve tumors that may have hybrid morphologic features.

<table>
<thead>
<tr>
<th>2012 WHO Classification of nerve sheath tumors</th>
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<tbody>
<tr>
<td>Schwannoma</td>
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<tr>
<td>Melanotic schwannoma</td>
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<tr>
<td>Neurofibroma</td>
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<tr>
<td>Perineurioma</td>
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<tr>
<td>Granular cell tumor</td>
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<tr>
<td>Dermal nerve sheath myxoma</td>
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<tr>
<td>Solitary circumscribed neuroma</td>
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<tr>
<td>Ectopic meningioma/meningothelial hamartoma</td>
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<tr>
<td>Nasal glial heterotopia</td>
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<tr>
<td>Benign Triton tumor</td>
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<tr>
<td>Hybrid nerve sheath tumors</td>
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<tr>
<td>Malignant peripheral nerve sheath tumor</td>
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<tr>
<td>Malignant granular cell tumor</td>
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<td>Ectomesenchymoma</td>
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Although these tumors may occur sporadically, several may be seen within the genetically determined disorders of neurofibromatosis (NF1, NF2, and schwannomatosis), as well as in multiple endocrine neoplasia 2b.

<table>
<thead>
<tr>
<th>General features of neurofibromatosis and MEN2b (Ref: Korf BR 2013)</th>
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<tbody>
<tr>
<td><strong>Disorder</strong></td>
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<tr>
<td>NF1</td>
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<tr>
<td>NF2</td>
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<tr>
<td>Schwannomatosis</td>
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<td>MEN2b</td>
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**Neurofibroma and neurofibroma variants**

*Describe the pathologic features of neurofibroma variants*

Neurofibroma is a benign and common peripheral nerve sheath tumor composed of a mixture of Schwann cells, fibroblasts, axons and perineurial cells. Although most occur sporadically as small subcutaneous tissue masses, these are the most common tumors associated with NF1, and may occur as deep seated masses. They occur in all age groups, in all races and equally in both sexes. In NF1, the plexiform and diffuse cutaneous forms occur early in life and are most likely congenital, whereas the localized forms often appear in the school-age years. Sporadic neurofibromas are slow growing and malignant transformation is exceptionally rare outside of the setting of NF.
### Forms of Neurofibromas (adapted from Cates and Coffin, PDP, 2012)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Location</th>
<th>Gross Pathology</th>
<th>Assn with NF1</th>
<th>Risk of malignancy</th>
</tr>
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<tbody>
<tr>
<td>Localized cutaneous</td>
<td>Dermis, subcutaneous</td>
<td>Nodular, soft, nonencapsulated</td>
<td>Very low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Diffuse cutaneous</td>
<td>Dermis, subcutaneous</td>
<td>Plaque-like, infiltrative, poorly defined</td>
<td>10%</td>
<td>Minimal</td>
</tr>
<tr>
<td>Localized intraneural</td>
<td>Deep</td>
<td>Well-defined, often fusiform</td>
<td>High, when multiple</td>
<td>Somewhat increased, but less frequent than plexiform</td>
</tr>
<tr>
<td>Plexiform intraneural</td>
<td>Deep, involves nerves/nerve plexi</td>
<td>Multinodular, “bag of worms”, often large, serpentine architecture</td>
<td>Very high (nearly 100%)</td>
<td>5-10%</td>
</tr>
<tr>
<td>Massive diffuse soft tissue</td>
<td>Deep</td>
<td>Very large, diffuse or plexiform, infiltrative</td>
<td>100%</td>
<td>Rare</td>
</tr>
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</table>

In general, neurofibromas have a gray to tan cut surface, but the gross appearance will vary depending upon the type (see table above). All neurofibromas share the basic histologic pattern of interlacing bundles of spindled cells, with a varying degree of loose to myxoid matrix with coarse collagen bundles. This often imparts a “shredded carrot appearance”. In some cases the degree of myxoid change is striking enough to raise the possibility of a myxoma. In other cases the tumors are more cellular and have a dense collagenous matrix rather than a loose myxoid matrix. Nuclei are ovoid to comma-shaped, and often there are scattered lymphocytes and mast cells. Unusual variants of neurofibroma include pigmented neurofibromas which contain melanin pigment in epithelioid or spindled tumor cells (Melan A positive), epithelioid neurofibromas and granular-cell neurofibromas.
Individual subtypes of neurofibroma have the following features:

**Localized cutaneous neurofibroma**: The most common type of neurofibroma is the localized cutaneous form; these tumors typically are small and polypoid (usually less than 2 cm), separated from the overlying epidermis by a Grenz zone and often have a densely collagenized stroma.

**Diffuse cutaneous neurofibroma**: Unlike the soft, freely mobile, well circumscribed and often polypoid localized cutaneous neurofibroma, the diffuse cutaneous form is large, thick, flat and grossly ill-defined. These lesions have a predilection for the head and neck, and histologically diffusely infiltrate the dermis and subcutaneous fat, without replacement. Meissner corpuscle-like bodies may be present.

**Localized intraneural neurofibroma**: The second most common type of neurofibroma, these lesions involve single nerves, causing fusiform, localized enlargement of the involved nerve. Ranging in size from small to very large, they are highly associated with NF1 when multiple. Any nerve, at any location and of any size can be involved, and deep lesions may cause pain. Histologically, nerve fascicles may be seen within these lesions on cross section. Unlike schwannoma, these tumors are intraneural rather than paraneural, and lack a thick tumor capsule.

**Plexiform intraneural neurofibroma**: These tumors are very highly associated with NF1, and in fact many investigators consider them to be pathognomonic for NF1, if strict criteria for plexiform architecture are applied. By definition a plexiform neurofibroma is a multinodular growth forming either along fascicles of a single large peripheral nerve or along a nerve plexus. This often imparts a gross appearance of tangled, myxoid, nodular nerves likened to a “bag of worms”, or a gross appearance of a plexus of branching nerves altered by multiple ovoid thickenings. Histologically these tumors typically have a prominent myxoid matrix, but may also have intermixed areas of diffuse neurofibroma.

**Massive diffuse soft tissue neurofibroma**: The rarest form of neurofibroma, it is pathognomonic for NF1. Extremely large, the tumor can cause massive enlargement or gigantism of the affected body part (in the leg this was historically referred to as “elephantiasis neuromatosa”).

**Differential Diagnosis and ancillary studies**: Immunohistochemistry typically reveals S100 staining of a subset of the tumor cells, staining which is generally less than that seen in schwannoma. Leu-7 and CD34 positivity is often seen, and EMA staining is usually absent, although it can be
sometimes seen in peripheral perineurial cells. If residual axons are present, they will stain with neurofilament protein.

The major differential diagnoses of neurofibroma include plexiform schwannoma, perineurioma, ganglioneuroma, plexiform fibrohistiocytic tumor, dermatofibrosarcoma protuberans and MPNST. The differential diagnosis with plexiform schwannoma and MPNST will be discussed later in this handout. Perineurioma, described in more detail later in the handout, tends to have more prominent whorling around nerve fibers, and is strongly EMA positive, unlike neurofibroma where EMA staining is absent or focal. Ganglioneuroma contains ganglion cells (which may be sparse) unlike neurofibroma. Plexiform fibrohistiocytic tumor can be distinguished by its immunohistochemical profile of positive actin and CD68 and negative staining for S100. DFSP can mimic diffuse neurofibroma, particularly when the typical storiform architecture is lacking, as in some cases of myxoid DFSP, as both have an infiltrative pattern. However, DFSP should lack S100 staining, and usually has more diffuse and strong CD34 staining.

**Atypical neurofibroma:** Schwann cells in neurofibroma may show nuclear pleomorphism, nuclear inclusions and degenerative hyperchromasia, similar to “ancient change” seen in schwannomas. In the absence of hypercellularity and mitotic activity, these findings do not denote malignancy. Mitotic activity, often seen with pleomorphism and increased cellularity is a worrisome feature and raises the possibility of transformation to MPNST. This will be discussed further in the MPNST section of the handout. Increased cellularity, in the absence of mitotic activity does not imply malignancy.
Neurofibromatosis 1 (NF1)

Discuss the criteria for diagnosis of NF-1, including genetic and pathologic features

Diagnostic Criteria for NF1

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>6 or more café-au-lait spots measuring at least 5 mm before puberty or 15 mm after puberty</td>
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<tr>
<td>Optic glioma</td>
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<tr>
<td>Characteristic skeletal dysplasia (long bone or sphenoid wing); pseudoarthrosis</td>
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<tr>
<td>Skin fold freckling of axillary or groin region</td>
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<tr>
<td>2 or more neurofibromas or one plexiform neurofibroma</td>
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<tr>
<td>2 or more Lisch nodules of the iris</td>
<td></td>
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<tr>
<td>First degree relative with NF1</td>
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</table>

NF1 is the most common of the neurofibromatosis, and is characterized by multiple non-tumor and tumoral manifestations, in addition to those fulfilling the diagnostic features in the table above:

**Café-au-lait spots**: Flat, pigmented macules; size, number and location do not correlate with severity of the underlying NF1. Often seen in early childhood.

**Skin fold freckling**: First seen in inguinal regions, later in axilla, often appear by 3-5 years of age

**Neurofibromas**: Numbers tend to increase after puberty, but the number of neurofibromas is variable in NF1

**Iris Lisch nodules**: melanocytic hamartomas; specific for NF1, require ophthalmologic slit lamp examination to be seen

**Optic gliomas**: Pilocytic astrocytomas of the optic nerve, chiasm and/or hypothalamus, seen in 15% of people with NF1.

**Skeletal dysplasia**: Can involve any bone; tibia is most common, and manifested clinically by limb bowing

**Cognitive impairment**: Approximately 50% of patients with NF1 have cognitive impairment (ADHD, intellectual impairment, learning disabilities, behavioral issues, visual-spatial problems)
**MPNST:** There is a lifetime risk of approximately 10% of developing an MPNST, which usually arise from a preexisting deep plexiform neurofibroma. This is often manifested by pain and rapid growth. When metastatic the outlook is very poor. Pathologic features of MPNST are described below.

**Other less common manifestations:** cerebral arteriopathy, pulmonary artery stenosis, juvenile myelomonocytic leukemia, GIST, subungual glomus tumors

**Genetic Features, pathogenesis and management of NF1**

NF1 is an autosomal dominant disorder with complete penetrance but with variable expression. Approximately half of patients represent new mutations of the NF1 gene and have unaffected parents. Somatic mosaicism can occur (“segmental NF1"), and is manifested by regional involvement. The risk of transmission to offspring of any individual with NF1, regardless of severity of the disease is 50%, and there is no way to predict the severity of the disease in the affected offspring.

NF1, found at 17q11.2, encodes the protein neurofibromin, which is an important tumor suppressor and is involved in controlling cell response to growth stimuli through stimulation of the conversion of Ras-GTP to Ras-GDP. Absence of neurofibromin leads to constitutive activation of the ras signaling pathway. The highest levels of neurofibromin levels are found in the central and peripheral nervous systems, reflecting the tissues most affected in this condition. Target cells in neurofibroma and MPNST are schwann cells that display mutations of both NF1 alleles, including the germline and acquired somatic mutation.

There is no cure for NF1, and current management consists of genetic counseling, surgical treatment of progressive lesions, and surveillance. Surgical treatment of neurofibromas is often necessary for debulking or cosmesis, and complete removal is often impossible for these lesions. Although there is no proven effective medical therapy, preclinical testing and clinical trials are exploring the use of therapies targeting the Ras pathway.

**Malignant peripheral nerve sheath tumor (MPNST)**

Malignant peripheral nerve sheath tumors (MPNST) are malignant tumors that arise from peripheral nerve or extraneural soft tissue and demonstrate
nerve sheath differentiation. MPNST is the preferred terminology for these tumors, which have formerly been called by a number of different names, such as neurofibrosarcomas and malignant schwannomas. Although these tumors mainly occur in adults, 10-20% occur in children (usually in the 2nd decade) and account for 5-7% of all pediatric sarcomas. They may occur earlier, and rarely can be present at birth. Interestingly, children with MPNST are less likely than adults to have NF1, although there are considerable differences in various series of pediatric MPNST (association with NF1 varying between 17 and 67%).

*List the minimal diagnostic criteria for MPNST*

There are no morphologic, immunohistochemical or molecular features that have been shown to be entirely specific, hence the diagnosis requires exclusion of other sarcomas that may involve major peripheral nerves. In general, any malignant spindle cell tumor arising in a patient with NF1 should be considered an MPNST until proven otherwise. In spindle cell tumors that do not demonstrate origin in a peripheral nerve the diagnosis is incumbent upon immunohistochemistry (S100 expression) and/or other evidence of Schwann cell or perineurial differentiation, as well as exclusion of spindle cell mimics (see differential diagnosis below).

**Grossly,** MPNST may be seen as arising from a plexiform neurofibroma or from a large peripheral nerve, in which case they may have a fusiform configuration. Tumors are usually large at diagnosis (greater than 5 cm). Necrosis and hemorrhage may be prominent.

**Microscopically,** MPNST are infiltrative neoplasms that can display a wide variety of appearances:

The “spindled cell” pattern is most common, and consists of a fibrosarcoma-like densely packed spindle cell proliferation, often with a herringbone architecture. Storiform and hemangiopericytoma-like vascular patterns may be seen, and the cell density in any given tumor may vary, bestowing an overall “marbled” appearance of alternating densely cellular and less densely cellular areas. Tumor cell nuclei are enlarged, vesicular or hyperchromatic, elongated, wavy or buckled, and the cytoplasm is usually sparse and amphophilic. Neuroid whorls (hypercellular whorling of tumor cells around vessels) may be seen, and tumor cells may infiltrate beneath vessel endothelial cells. Mitotic figures are almost invariably present, and may be numerous, with most MPNST exhibiting 4 or more mitoses/HPF. Necrosis may be extensive, and pleomorphism is commonly seen, usually in the form of scattered giant cells.
**Immunohistochemistry**

There is no single immunohistochemical stain that is sensitive or specific for MPNST. However immunohistochemistry can be quite useful in bolstering the diagnosis by excluding other sarcomas. The most sensitive stain for MPNST, (excepting the ubiquitously expressed vimentin) is S100 (positive in 30-67% of tumors), and the degree of staining generally diminishes as tumor grade increases. S100 staining is usually focal and weak to moderate. Other stains which may be focally positive include TLE1, GFAP, Leu7, laminin and collagen type 4. EMA, CD34 and Glut-1 may stain MPNST’s with perineurial differentiation. Wide-spectrum cytokeratins are occasionally positive.

**Electron microscopy**

Although ultrastructural features of nerve sheath differentiation such as basal lamina, long spacing collagen (Luse bodies) and intertwined cytoplasmic processes are seen in benign and well differentiated tumors, these findings are generally inconspicuous or completely absent in the more undifferentiated MPNST’s, which may occasionally display wisps of basal lamina and rudimentary cell junctions.

**Grading**

Most MPNSTs are high grade sarcomas. However, there is no generally accepted standardized grading system for MPNST. By the time of diagnosis, most MPNSTs have cytologic atypia, are densely hypercellular and fascicular and have brisk mitotic activity; all features of high grade tumors. A smaller subset (approximately 15%), display lower cellularity and appear to be in transition from a pre-existing neurofibroma.

**Molecular Genetics**

These tumors tend to have complex, aneuploid karyotypes, and lack pathognomonic translocations. There are frequent losses of 9p21 and 17p. Both NF1 related and unrelated tumors are associated with aberrations in the TP53 and RB cell cycle regulation pathways.
Describe the variants of MPNST and the differential diagnosis of MPNST

Histologic variants:

**Small cell variant**: Rare, composed of sheets and nests of small round cells with primitive neural differentiation, and occasional rosettes. This form of MPNST is more common in younger patients and has no association with NF1. The small round cell elements are generally negative for CD99.

**Glandular MPNST**: Mucinous glandular differentiation can be seen in both benign and malignant peripheral nerve sheath tumors, and the epithelial component is usually benign. This can cause diagnostic confusion with biphasic synovial sarcoma; however, synovial sarcoma would lack evidence of a preexisting origin from a neurofibroma or nerve, lack goblet cells, and often show cytokeratin staining in the spindle cell population as well as in the glands.

**Malignant triton tumor**: MPNST with variable numbers of rhabdomyoblasts, most likely due to rhabdomyoblastic transformation of neoplastic Schwann cells. This tumor should display focal desmin or MSA staining, as well as focal myogenin or MyoD1 reactivity. The prognosis of this tumor is poor.

In addition, some MPNST’s may contain other heterologous elements, such as chondroid tissue, osteoid, and angiosarcomatous elements.

**Deep epithelioid MPNST**: These rare tumors are composed mainly or entirely of epithelioid cells, are unassociated with NF1, and most originate from a nerve or from an existing schwannoma. Histologically the tumor cells have abundant eosinophilic or amphophilic cytoplasm and vesicular nuclei, often with prominent nuclei, raising the differential diagnoses of melanoma, proximal type epithelioid sarcoma and rhabdoid tumor. Immunohistochemistry reveals strong and diffuse S100 staining in approximately 80% of these tumors, with negative results for melanoma markers and cytokeratins. INI1 may be lost in a subset of cases.

Differential Diagnosis of MPNST with neurofibroma

One of the most challenging issues in peripheral nerve tumor pathology is the distinction between an atypical yet benign neurofibroma and a low grade
MPNST. Although most neurofibromas are histologically patently benign, and most MPNSTs are clearly high grade and malignant, there is a histologic continuum between the two extremes, as one might expect from a malignancy that often originates from a preexisting neurofibroma, particularly in the setting of NF1. There is no universally accepted set of "minimal diagnostic criteria" for MPNST, and there are histologically borderline cases which will have an uncertain biologic potential. Helpful points include:

- Nuclear atypia (pleomorphism, hyperchromasia) whether focal or diffuse is common in benign neurofibromas, and in the absence of hypercellularity and/or mitotic activity is not worrisome.

- Hypercellularity alone, without nuclear atypia and mitotic activity does not denote malignancy.

- Mitotic activity alone may not be enough to diagnose malignancy, but should be considered a very worrisome feature, and additional sampling may be necessary. Usually mitotic activity is seen in areas of higher cellularity, and may herald malignant degeneration.

- A tumor with diffuse nuclear hyperchromasia, nuclear enlargement (3X the size of a normal schwann cell nucleus), mitotic activity and hypercellularity should be considered to be an MPNST.

- The term "neurofibroma with atypical features" would apply to tumors with atypical features that do not meet the full criteria for malignancy listed above.

- Mitotic activity is not required to diagnose malignancy. Tumors with marked hypercellularity, atypia and a fascicular architecture (as opposed to the haphazard pattern of neurofibroma) are MPNST, even if they lack appreciable mitotic activity. However, as described above, any of these features alone is insufficient to diagnose malignancy.

**Differential Diagnosis of MPNST with other sarcomas**

Many tumors can mimic the histologic appearance of MPNST; the most common being perineurioma, cellular schwannoma (these are described in detail later in this workshop), synovial sarcoma, spindle cell
rhabdomyosarcoma, and fibrosarcoma. Most can be excluded with targeted molecular diagnostic and immunohistochemical studies.

**Schwannoma, NF-2, and Carney complex**

*Describe the pathologic features of schwannoma variants*

Like neurofibromas, schwannomas (synonyms neurolemmoma/neurinoma) are benign tumors of peripheral nerve. However, the similarities between these two tumor types largely end there. Whereas neurofibromas contain a complex mixture of cell types, schwannomas are composed solely of well-differentiated (albeit neoplastic) Schwann cells.

Schwannomas are typically encapsulated globular lesions that often ‘push’ the associated nerve to one side rather than infiltrating the nerve in the manner characteristic of neurofibromas.

![Diagram of Neurofibroma and Schwannoma](image.png)

The neurofibroma incorporates axons, but the schwannoma displaces normal elements of the nerve to one side.
The microscopic appearance of conventional schwannoma is characterized by a variable admixture of compact spindled (Antoni A) areas and hypocellular, microcystic (Antoni B) areas rich in macrophages and collagen fibers. A well-formed collagenous capsule is a consistent finding as well as hyalinized vessels.

By immunohistochemistry, schwannomas typically show diffuse, strong expression of S100 protein and abundant pericellular collagen type IV, consistent with the presence of a continuous pericellular basal lamina. Glial fibrillary acid protein (GFAP) is expressed in a subset of schwannomas. Recent markers frequently positive in schwannomas include podoplanin, calretinin, and SOX10. Very rarely, otherwise typical schwannomas may show anomalous expression of cytokeratins. Such tumors are always strongly GFAP-positive, suggesting cross reactivity of cytokeratin antibodies with GFAP, rather than true protein expression.

Unlike neurofibroma, neurofilament protein staining is usually limited to entrapped axons at the periphery of the tumor, although some recent studies suggest that the presence of intralesional axons is actually more frequent than previously reported.

**Further, malignant transformation of schwannomas is exceedingly rare.**

*Although uncommon, some schwannoma variants are periodically encountered:*

1) cellular schwannomas (a benign variant with cellularity higher than a conventional schwannoma)
2) plexiform schwannomas (schwannomas with a growth pattern reminiscent of plexiform neurofibromas)
3) melanotic schwannomas (schwannomas containing extensive melanin and at times psammoma bodies)

*The primary significance of these variants is that they may be mistaken for a more aggressive tumor type (cellular schwannomas) or herald the presence of a genetic disease (plexiform schwannomas, melanotic schwannomas).*

**Cellular schwannoma,** relatively uncommon, is an important variant of schwannoma to recognize, because its high cellularity, fascicular growth pattern, increased mitotic activity, and occasional locally destructive behavior, including bone erosion, often prompt consideration of malignancy. **Cellular schwannoma is defined as a schwannoma composed almost entirely of a compact, fascicular proliferation of well differentiated,**
cytologically bland Schwann cells, lacking Verocay bodies, and showing no more than very focal Antoni B pattern growth (<10% of the tumor area). Important clues to this diagnosis include the presence of foamy histiocyte aggregates, a well-formed capsule containing lymphoid aggregates, and diffuse strong S100 protein and pericellular collagen IV expression. Diffuse S100 protein expression is exceedingly uncommon in spindled MPNST, and this finding should always raise the possibility of cellular schwannoma. Cytokeratin immunoreactivity may be seen in some cellular schwannomas, and may represent cross reactivity with GFAP, as mentioned above. Importantly, cellular schwannomas lack expression of smooth muscle actin, desmin, CD117 and DOG1, allowing exclusion of other important tumors in its differential diagnosis, leiomyosarcoma and GIST, respectively. Cellular schwannomas, despite their occasional alarming cellularity, lack malignant potential for practical purposes and never metastasize. Local recurrence is variable (5–40%) and may be higher than in conventional schwannomas. This may be related in part to location, given the propensity for deep anatomic regions that are not always amenable to gross total resection. However, even recurrent lesions grow slowly and do not result in death. Mitotic activity is usually less than 5 per 10 high-power fields. However, brisk mitotic activity, even in excess of 10 per 10 high-power fields, may be present in rare instances, and if other features diagnostic of cellular schwannoma are present, this proliferative activity is still compatible with a benign diagnosis.

**Plexiform schwannoma** is a distinctive subtype of schwannoma that usually occurs in superficial (cutaneous or subcutaneous) locations and is defined by a plexiform (intraneural-nodular) pattern of growth. Although they may be associated with schwannoma predisposition syndromes such as NF2 and schwannomatosis, the association is weak (approximately 5% of cases).

These tumors may be less circumscribed than conventional schwannoma, or even lack a capsule. The tumors are usually composed of Antoni A patterns. Neurofilament protein immunoreactive axons are usually identified within the lesion. More problematic are the rare plexiform schwannomas that arise in deep anatomic locations, in soft tissue or major peripheral nerves, since they may demonstrate increased cellularity and mitotic activity and thus, may be difficult to distinguish from MPNST. Although these tumors have a negligible malignant potential, local recurrence may be relatively high, occurring in approximately half of the cases. Again, the presence of widespread S100, collagen IV immunoreactivity or basal lamina by electron microscopy is reassuring.
Melanotic schwannoma is a rare, distinctive, potentially malignant neoplasm characterized by epithelioid cells with variably sized nuclei and marked accumulation of melanin in neoplastic cells and associated melanophages. The main differential diagnosis is with other melanin-producing neoplasms, in particular melanoma. The presence of psammoma bodies in these tumors (i.e., psammomatomous melanotic schwannoma) is associated with approximately half the cases with Carney complex.

Schwannomas are commonly encountered in the general population as solitary lesions. However, these peripheral nerve sheath tumors also occur multiply in patients with three distinct genetic diseases:

- Neurofibromatosis type 2 (NF2)
- Carney complex
- Schwannomatosis

Discuss the criteria for diagnosis of NF-2, including genetic and pathologic features

NF2, the most common genetic disease associated with schwannoma pathogenesis, is estimated to affect 1 in 25,000 newborn infants.

- Schwannomas developing in NF2 patients typically arise in the vestibular branch of the eighth cranial nerve and may be unilateral or bilateral.
- Multiple schwannomas are also commonly found on cranial nerves or spinal nerve roots in these patients as well as cutaneously, where they are often plexiform.
- In addition to schwannomas, NF2 patients are prone to the development of meningiomas and, less commonly, ependymomas.
- Cataracts, retinal hamartomas and combined pigment epithelial and retinal hamartomas are also commonly found in these patients.

1) Like NF1, NF2 is inherited in an autosomal dominant fashion, which is consistent with the NF2 gene encoding a tumor suppressor.
2) The NF2 gene also has a similarly high rate of de novo mutation, resulting in about 50% of infants with NF2 being born into families with no previous history of the disease; further, about a third of patients presenting with clinical features of NF2 demonstrate mosaicism for this mutation.
3) NF2 is completely penetrant in virtually all patients by the time they are 60 years old.
The NF2 tumor suppressor gene, which is located on chromosome 22 (22q12.2), was cloned in 1993. This locus spans 93,083 base pairs and includes 17 exons. The NF2 gene produces at least 10 protein isoforms via a combination of alternative splicing and the use of multiple transcription initiation sites.

However, isoforms I and II, which have distinct carboxy terminal sequences produced by alternative splicing of exons 16 and 17, respectively, predominate. The proteins encoded by the NF2 gene are highly unusual in that they do not contain catalytic domains such as are present in neurofibromin and many other tumor suppressors. These polypeptides are instead structurally similar to three molecules in the protein 4.1 superfamily that are known as ezrin, radixin and moesin (the ‘ERM’ proteins). These three ERM proteins link the actin cytoskeleton to membrane-spanning proteins, thereby organizing complex membranous domains and regulating cellular adhesion, migration, cellular morphology, exocytosis and endocytosis. Because of this structural similarity, the NF2 protein was dubbed ‘merlin’ (moesin-, ezrin-, radixin-like protein); as loss of the NF2 gene is associated with schwannoma pathogenesis, the NF2 protein is also sometime referred to as schwannomin.

In keeping with clinical observations suggesting that merlin is a tumor suppressor, germline DNA from NF2 patients contains a mutated NF2 gene and a functional wild-type allele while schwannomas developing in these patients carry two mutated NF2 genes. The importance of NF2 mutations in schwannoma pathogenesis is further demonstrated by the observation that the overwhelming majority of sporadic schwannomas have lost the expression of merlin, but not other ERM proteins.
Discuss the criteria for diagnosis of Carney complex and melanotic schwannoma

Background

Carney complex (CNC) is a rare multiple neoplasia syndrome first described by Dr. J. Aidan Carney in 1985 as “the complex of myxomas, spotty pigmentation, and endocrine overreactivity” and inherited in an autosomal dominant manner; Dr. Carney recognized that patients with syndromes that had been previously described as LAMB (lentigines, atrial myxoma, myxoid neurofibroma, and ephelide) or NAME (nevus, atrial myxoma, blue nevi) had the same condition. To this date, over 500 patients of diverse ethnicity from all continents have been registered by the NIH-Mayo Clinic (USA) and the Cochin Hospital (France); 43% are males and 57% are females; approximately 70% are familial cases.

Diagnosis and clinical manifestations of Carney complex

The diagnosis of CNC is made if two or more major manifestations of the syndrome are present (Table). These must be confirmed by histology, biochemical testing, and imaging. However, one can also make the diagnosis when only one of the major criteria is present if the patient is a carrier of a known inactivating mutation of PRKAR1A. In addition, a considerable number of clinical and biochemical manifestations listed in the table are suggestive, but not diagnostic, of CNC.
## Diagnostic criteria for Carney complex (CNC)

<table>
<thead>
<tr>
<th><strong>Major diagnostic criteria for CNC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosal)</td>
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<tr>
<td>2. <strong>Myxoma</strong>&lt;sup&gt;a&lt;/sup&gt; (cutaneous and mucosal)</td>
</tr>
<tr>
<td>3. Cardiac myxoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4. Breast myxomatosis&lt;sup&gt;a&lt;/sup&gt; or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis</td>
</tr>
<tr>
<td>5. PPNAD&lt;sup&gt;a&lt;/sup&gt; or paradoxical positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddle’s test</td>
</tr>
<tr>
<td>6. <strong>Acromegaly</strong> due to GH-producing adenoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7. LCCST*or characteristic calcification on testicular ultrasound</td>
</tr>
<tr>
<td>8. Thyroid carcinoma* or multiple, hypoechoic nodules on thyroid ultrasound in a young patient</td>
</tr>
<tr>
<td>9. Psammomatous melanotic schwannomas&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10. Blue nevus, epithelioid blue nevus*</td>
</tr>
<tr>
<td>11. Breast ductal adenoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>12. Osteochondromyxoma&lt;sup&gt;a&lt;/sup&gt;</td>
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<table>
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<tr>
<th><strong>Supplementary criteria</strong></th>
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<tbody>
<tr>
<td>1. Affected first-degree relative</td>
</tr>
<tr>
<td>2. Inactivating mutation of the PRKAR1A gene</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Findings suggestive of or possibly associated with CNC, but not diagnostic for the disease</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intense freckling (without darkly pigmented spots or typical distribution)</td>
</tr>
<tr>
<td>2. Blue nevus, common type (if multiple)</td>
</tr>
<tr>
<td>3. Café-au-lait spots or other &quot;birthmarks”</td>
</tr>
<tr>
<td>4. Elevated <strong>IGF-1</strong> levels, abnormal GTT, or paradoxical GH response to TRH testing in the absence of clinical acromegaly</td>
</tr>
<tr>
<td>5. Cardiomyopathy</td>
</tr>
<tr>
<td>6. Pilonidal sinus</td>
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<tr>
<td>7. History of Cushing’s syndrome, acromegaly, or sudden death in extended family</td>
</tr>
<tr>
<td>8. Multiple skin tags or other skin lesions; lipomas</td>
</tr>
<tr>
<td>9. Colonic polyps (usually in association with acromegaly)</td>
</tr>
<tr>
<td>10. <strong>Hyperprolactinemia</strong> (usually mild and almost always combined with clinical or subclinical acromegaly)</td>
</tr>
<tr>
<td>11. Single, benign thyroid nodule in a young patient; multiple thyroid nodules in an older patient (detected on ultrasound)</td>
</tr>
<tr>
<td>12. Family history of carcinoma, in particular of the thyroid, colon, pancreas, and ovary; other multiple benign or malignant tumors</td>
</tr>
</tbody>
</table>

<sup>a</sup>After histological confirmation
Cutaneous manifestations
Pigmented skin lesions are reported in the majority of CNC patients (over 80%).

They constitute one of the three major criteria of CNC and are diagnostically very important because they are easily recognizable and occurring early in life, they may lead to early detection of a potentially life-threatening disease.

The most common skin lesions are lentigines (they are present in 70–75% of cases). Morphologically, lentigines are flat, poorly circumscribed, brown-to-black macules usually measuring less than 0.5 cm in diameter. Histologically, lentigines show hyperpigmentation of the basal cell layer associated with melanocytic hyperplasia and hypertrophy. In contrast, the pigmentation in common freckles is the result of increased melanin production, usually without melanocytic hyperplasia. Even though lentigines may be the first sign of CNC at birth, they usually do not acquire their typical intensity and characteristic distribution (lips, conjunctiva, and inner and outer canthi; vaginal and penile mucosa) until the late prepubertal and early peripubertal period.

The second most frequent skin manifestations in CNC patients are blue nevi, and in particular, epithelioid blue nevi, followed by cutaneous myxomas. Early identification of cutaneous myxomas is essential since it is estimated that almost 80% of CNC patients with a life-threatening cardiac myxoma had presented earlier in life with cutaneous myxoma.

Other CNC-related skin manifestations include: café-au-lait spots (typically less pigmented than those seen in Mc-Cune Albright syndrome) or depigmented lesions that can also be present at birth or develop during childhood; melanocytic and atypical nevi, and the so-called Spitz nevus.

Neoplasms in Carney complex
Cardiac myxomas, which can appear as early as in infancy, are responsible for over 50% of the disease-specific mortality of CNC patients. Early detection and regular screening for cardiac myxomas by echocardiography is essential, as these tumors can lead to sudden death by embolism, strokes, or cardiac failure. Cardiac myxomas are the most common, clinically significant non-cutaneous lesions in CNC patients.

Pigmented nodular adrenocortical disease (PPNAD) is the most frequent endocrine manifestation in CNC patients. Adrenocorticotropic hormone-independent Cushing syndrome (CS) is present in 25–30% of CNC patients. Pigmented nodular adrenocortical disease is named after the macroscopic
appearance of the adrenal glands that is characterized by small, cortisol-producing, pigmented micronodules (less than 1 cm in diameter) of the adrenal cortex. Diagnosis of CS due to PPNAD is often difficult because hypercortisolism can develop progressively over years and may be periodic: cyclical and atypical CS is more often the rule, rather than the exception among patients with CNC. Pathological investigation reveals that adrenal glands from patients with PPNAD are usually normal in size and weight; it is for this reason that one out of three patients has essentially normal appearing adrenal glands on computed tomography (CT scan). The remaining patients may have visible round micronodules (smaller than 1 cm in diameter) or rarely, macronodules (larger than 1 cm) within the background of hyperplasia.

Psammomatous melanocytic schwannoma (PMS) was present in 8% of CNC patients studied by Bertherat et al., and four patients died of metastatic PMS. Psammomatous melanocytic schwannoma may occur anywhere in the peripheral nervous system, but it is most frequently found in the gastrointestinal tract (esophagus and stomach) and the paraspinal sympathetic chain. Schwannomas in CNC are characterized by their heavy pigmentation (melanin), frequent calcifications, and multicentricity. Psammomatous melanocytic schwannoma is unlike any of the schwannomas.

In contrast to conventional schwannomas, melanotic schwannomas usually lack Verocay bodies, microcysts, a well formed capsule and thick-walled hyalinized vessels. Psammoma bodies may be focal and only identifiable after extensive search. However, their recognition is important since approximately half of patients with PMS have CNC, and the syndrome association is even higher when multiple tumors are present. In addition these tumors frequently contain large cytoplasmic vacuoles simulating adipose tissue.

Another important distinction with conventional schwannoma is that a subset of melanotic schwannomas (up to 15% of reported cases) is associated with malignant clinical behavior. Strict criteria of malignancy in melanotic schwannoma are not well developed, although a combination of worrisome histologic features (large vesicular nuclei with macronucleoli, brisk mitotic activity, and necrosis) raises concern of aggressive behavior.

The differential diagnosis of melanotic schwannoma is largely restricted to melanocytic tumors ranging from melanocytoma to primary and metastatic melanoma. Melanocytic immunohistochemical markers (e.g., S100, melanA, HMB45) are not useful in this distinction, since they are frequently expressed in both tumor categories. The identification of pericellular basement membrane by histochemical (reticulin) and immunohistochemical (collagen
IV, laminin) stains or by electron microscopy is more specific for melanotic schwannoma, although this important diagnostic feature is not as accentuated as in conventional schwannomas.

Genetic linkage analysis identified two independent loci for CNC, CNC1 located on chromosome 17p22–24 and CNC2 located on chromosome 2p16. The genetic defect responsible for CNC at locus 2p16 remains unknown. In most cases, CNC is caused by inactivating mutations in the regulatory subunit type 1 alpha gene (PRKAR1A) located at 17q22–24 which encodes the most widely expressed of the protein kinase A (PKA) regulatory subunits. Thus, PRKAR1A is a key component of the cAMP signaling pathway. PRKAR1A’s genomic region is approximately 21 kb long and the open reading frame contains 11 exons that code for a protein that totals 384 amino acids. The peptide consists of a dimerization/docking domain and two cAMP binding domains (A and B) that are essential for its function within the PKA tetramer.

**Schwannomatosis:**

*RECOGNIZE ADDITIONAL SYNDROMES INCLUDING SCHWANNOMATOSIS AND MEN 2B*

Schwannomatosis is the most recent addition to the group of neurofibromatosis syndromes. The incidence is difficult to ascertain since it is likely under recognized; however, it may be similar to that of NF2. Defining features of this syndrome are that the schwannomas spare the vestibular nerves and patients often have significant associated pain, which may be debilitating. Meningiomas and infrequently ependymomas have also been reported in these patients.

Approximately 10% of schwannomatosis patients have a family history while 90% are sporadic. Genetic studies indicate that germline mutations in the *SMARCB1* tumor suppressor gene occur in 40-50% of familial cases and 8-10% of sporadic cases. While germline *SMARCB1* abnormalities also cause inherited predisposition to highly malignant rhabdoid tumors, it is very rare to see both rhabdoid tumors and schwannomas in the same patient or family. The factors responsible for the given phenotypes are unclear. There appear to be more mutations and/or deletions leading to a complete knockout of the *SMARCB1* gene product in those with rhabdoid tumors while inherited mutations found in schwannomatosis are more likely to be non-truncating (missense or splice-site) mutations.
In schwannomatosis patients with \textit{SMARCB1} mutations, tumorigenesis is thought to occur through a four-hit, three-step model, resulting in loss of functional \textit{SMARCB1} and \textit{NF2} gene products:

**Hit 1**- Germline mutation in \textit{SMARCB1} on one copy of chromosome 22  
**Hit 2 and 3**- Loss of all or a portion of the other copy of chromosome 22 that contains the second copy of \textit{SMARCB1} plus one copy of the \textit{NF2} gene  
**Hit 4**- Mutation of the remaining \textit{NF2} allele

Despite identification of germline \textit{SMARCB1} mutations, a large portion of familial and the majority of sporadic schwannomatosis patients have no know causative mutations. Reports in 2013 and 2014 have demonstrated germline mutations in the \textit{LZTR1} gene, a tumor suppressor gene and driver in glioblastomas, in a subset of patients with schwannomatosis.

Diagnostic criteria set forth in 2005 by MacCollin proposed that no cases should be diagnosed before the age of 30 years to document the absence of vestibular schwannomas and thus a diagnosis of \textit{NF2}. The diagnostic criteria proposed from the 2011 International Schwannomatosis Workshop include both molecular and clinical methods for diagnosis without an age cut off:

| Molecular Diagnosis | Two or more pathologically proved schwannomas or menigiomas AND genetic studies of at least two tumors with LOH for chromosome 22 and two different \textit{NF2} mutations; if there is a common \textit{SMARCB1} mutation, this defines \textit{SMARCB1} schwannomatosis  
| | One pathologically proved schwannoma or menigioma AND germline \textit{SMARCB1} pathogenic mutation |

| Clinical Diagnosis | Two or more non-intradermal schwannomas, one with pathological confirmation, including no bilateral vestibular schwannoma by high-quality MRI.  
| | One pathologically confirmed schwannoma or intracranial menigioma AND affected first-degree relative  
| | Consider possible diagnosis if there are two or more non-intradermal tumors but none has been pathologically proven to be schwannoma |

| Patient Exclusion Criteria | Germline pathogenic \textit{NF2} mutations  
| | Fulfill diagnostic criteria for \textit{NF2}  
| | First-degree relative with \textit{NF2}  
| | Schwannomas in previous field of radiation therapy only |
There are no specific histologic features diagnostic of syndrome-associated schwannomas. However, the presence of abundant myxoid stroma and/or hybrid tumors (benign nerve sheath tumors with characteristic features of both neurofibromas and schwannomas) should alert the pathologist to the possibility of an association with any of the neurofibromatoses (NF1, NF2 and schwannomatosis) as opposed to the sporadic schwannoma. Additionally, a “mosaic pattern” of staining for SMARCB1/INI1, in which some tumor cells are positive and some negative, is suggestive of a tumor related to NF2 and/or familial schwannomatosis (>90%, NOTE that this staining pattern is not specific for schwannomatosis). This mosaic pattern of staining is unusual (5%) in non-syndromic tumors.

**Multiple Endocrine Neoplasia, Type 2b**

Multiple endocrine neoplasia, type 2b (MEN 2b) is an autosomal dominant syndrome characterized by a marfanoid body habitus, skeletal anomalies and the development of endocrine neoplasms including medullary thyroid carcinoma and pheochromocytoma. The peripheral nervous system is also affected by hamartomatous proliferations of multiple mucosal neuromas and intestinal ganglioneuromatosis. Ninety-five percent of MEN 2b cases result from a single amino acid substitution in the RET protein resulting in activation of the RET proto-oncogene.

Mucosal neuromas are often the first sign of disease and occur in nearly all patients as bumps on the lips, tongue and buccal mucosae. The eyelids, conjunctivae and corneas may also develop neuromas and infants may be unable to make tears. These neuromas are important from a diagnostic standpoint because they are easily biopsied. Correct identification is crucial to alert the clinician to the possibility of MEN 2b so that proper diagnosis and cancer screening may be instituted. Histologically, mucosal neuromas demonstrate tortuous, enlarged nerves with thickened perineurium beneath the mucosal surface. Of note, there is no reactive fibrosis or inflammation as would be expected in traumatic neuromas (see discussion of traumatic neuroma below).

Children may also present with gastrointestinal signs and symptoms such as constipation, diarrhea or megacolon due to diffuse intestinal ganglioneuromatosis. Histologic findings are similar with tortuous and enlarged submucosal and myenteric plexuses in the intestine. These findings on endoscopic biopsy are not specific for MEN 2b since other syndromes may have intestinal ganglioneuromas including Cowden, Juvenile polyposis and NF1. However, if the findings are extensive and involve all of the intestinal layers, this is relatively specific for MEN 2b.
Benign nerve sheath-derived neoplasms

DESCRIBE THE PATHOLOGIC FEATURES OF BENIGN NERVE SHEATH NEOPLASMS (PERINEURIOMA, NEUROTHEKEOMA, AND NERVE SHEATH MYXOMA).

Introduction
There are relatively few benign nerve sheath-derived neoplasms. While granular cell tumors and ganglioneuromas deserve mention, they are quite distinct histologically and usually do not present a diagnostic dilemma. In contrast, perineurioma, neurothekeoma and nerve sheath myxoma are uncommon. The histologic features and anatomic location of these lesions necessitate a broad differential diagnosis that relies upon knowledge of soft tissue pathology, neuropathology and/or dermatopathology, which adds to the difficulty in diagnosis.

Perineurioma
A perineurioma is composed exclusively of neoplastic perineurial cells. Perineurial differentiation must be shown for diagnosis by immunohistochemistry (IHC) and/or electron microscopy (EM). EMA is most useful to demonstrate perineurial lineage; however, due to the long, thin cell processes EMA staining may appear “patchy”. Claudin-1 and GLUT-1 are also positive while S-100, GFAP and CD57 are negative. By EM, cells show long, thin, bipolar cytoplasmic processes; subplasmalemmal pinocytotic vesicles; poorly formed desmosomes; and a discontinuous external lamina. The most common cytogenetic abnormalities in perineuriomas involve loss of chromosome 22 involving the NF2 locus. Chromosomal rearrangements and/or deletions involving 10q have been shown in sclerosing perineuriomas.

Perineuriomas are rare, especially in childhood. They have a wide anatomic distribution and are usually divided into intraneural and soft tissue subtypes. Intraosseous and intestinal perineuriomas have been reported.

Intraneural perineuriomas are the most common type encountered in the pediatric population. The lesions present as a painless mass in an extremity with associated muscle weakness and atrophy. Grossly the lesions produce a segmental, firm, sausage-shaped enlargement of the nerve. Histologic features are best appreciated on nerve cross-section where perineurial cells are seen circumferentially enwrapping individual, preexisting Schwann cell-axon complexes. These configurations are termed “pseudo-onion bulbs” due to their resemblance to true Schwann cell-derived onion bulbs present in hypertrophic neuropathies. In intraneural perineuriomas, EMA highlights the encircling perineurial cells while neurofilament and S100 highlight the nerve...
fiber “center” of the pseudo-onion bulb. The main differential diagnosis includes other lesions that cause segmental nerve involvement such as hypertrophic neuropathies, neurofibromas and traumatic neuromas.

Soft tissue perineuriomas are subdivided into conventional, reticular and sclerosing variants. Of these, the sclerosing subtype is the only to present in the pediatric population with any frequency, usually in adolescents. They present as painless, well-circumscribed, unencapsulated masses on the fingers or hands and are centered in the dermis or subcutis. The cells are a mixture of bland epithelioid and spindle-shaped cells with small nuclei embedded in a collagenous matrix. Cells are arranged in cords, arcades and whorls. The most important differential diagnosis for this lesion is epithelioid sarcoma due to its aggressive nature. While epithelioid sarcoma is also positive for EMA, the presence of cytologic atypia, central necrosis, cytokeratin positivity and loss of SMARCB1/INI1 staining help to differentiate it from perineurioma. Other lesions in the differential include fibroma of tendon sheath, fibrotic tenosynovial giant cell tumor, sclerotic fibromas associated with Cowden syndrome, sclerosing adnexal tumors and glomus tumors.

**Neurothekeoma and Nerve sheath myxoma**

A historical perspective on the distinction between these lesions is interesting and has led to confusion concerning terminology and classification. Nerve sheath myxoma and neurothekeoma are both dermal/subcutaneous lesions originally described in 1969 and 1980 respectively. However, subsequent studies suggested that these tumors represented “myxoid” and “cellular” forms of the same entity. However, growing evidence over time has firmly established that these lesions are in fact distinct. The table below highlights the differences between nerve sheath myxoma and neurothekeoma:
<table>
<thead>
<tr>
<th>Feature</th>
<th>Nerve Sheath Myxoma</th>
<th>Neurothekeoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Young and middle-aged adults</td>
<td>Children and young adults</td>
</tr>
<tr>
<td>Gender</td>
<td>Equal ratio</td>
<td>2:1, female/male</td>
</tr>
<tr>
<td>Location</td>
<td>Distal extremities</td>
<td>Face, shoulder, upper arms</td>
</tr>
<tr>
<td>Histology</td>
<td>Multiple nodules/lobules with fibrous borders; spindled,</td>
<td>Multiple nodules/lobules without fibrous borders;</td>
</tr>
<tr>
<td></td>
<td>stellate and epithelioid cells in cords, rings, syncytial-like arrangements; routinely abundant myxoid matrix</td>
<td>epithelioid and spindled cells; stroma often collagenous with variable myxoid matrix</td>
</tr>
<tr>
<td>Immunoreactivity</td>
<td>S-100 and GFAP positive</td>
<td>S-100 always and GFAP usually negative</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Classification</td>
<td>Schwann cell tumor</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Adapted from the AFIP Atlas of Tumor Pathology, Series 4, Tumors of the Peripheral Nervous System

Nerve sheath myxomas demonstrate Schwann cell differentiation with positivity for S-100, GFAP, CD57 and collagen type 4. Of note, EMA highlights perineurial cells at the periphery of the tumor nodules, but staining should be absent within the lobules. The differential diagnosis includes other superficial myxoid lesions including focal mucinosis and superficial angiomyxoma as seen in Carney complex. Conventional schwannoma with abundant myxoid matrix may be confused with nerve sheath myxoma. While the immunohistochemical profile is the same, conventional schwannomas will show encapsulation and at least focal diagnostic features such as Antoni A tissue and Verocay bodies which are absent in nerve sheath myxoma.

Neurothekeoma does not demonstrate Schwann cell differentiation. The tumors are positive for CD63, CD99, CD68, NKI-C3 and CD10. Recent reports show that up to 80% are positive for microphthalmia transcription factor. There may be focal staining with SMA. The tumor cells are negative for S-100, GFAP and collagen type 4. The differential diagnosis includes superficial fibrohistiocytic tumors but these lesions lack the lobulated growth pattern and are more infiltrative along the periphery. Melanocytic lesions can be recognized by staining with S-100 and usually a junctional component. Epithelioid sarcoma can be distinguished by the presence of cytologic atypia, central necrosis, cytokeratin and EMA positivity and loss of SMARCB1/INI1 staining.
Mass-forming reactive and hamartomatous lesions involving peripheral nerves

DESCRIBE THE PATHOLOGIC FEATURES OF MASS-FORMING REACTIVE AND HAMARTOMATOUS LESIONS INVOLVING PERIPHERAL NERVES

Introduction
There are numerous reactive, hamartomatous, and infectious lesions of nerve, which may present as mass-forming lesions. A full discussion is beyond the scope of this handout and only selected disorders are discussed below.

Neuromuscular choristoma
Neuromuscular choristoma (NMC), also called neuromuscular hamartoma, is a rare lesion defined by admixed mature skeletal muscle fibers within peripheral or cranial nerves. There are isolated reports of involvement with smooth muscle fibers as well. Most patients present in childhood or the neonatal period with sensorimotor defects. Grossly, NMC is a nodular, firm, gray-brown mass lying within or attached to a nerve. The muscle fibers are intimately admixed with nerve fibers and may involve the epineurium as well. There are variable amounts of fibrous tissue present and a fibromatosis-like picture may be seen in the affected area during or after initial surgery. The differential diagnosis includes rhabdomyomatous mesenchymal hamartoma which may have associated nerve fibers, but is found within the skin and is not associated with a sizeable nerve. Peripheral nerve sheath tumor with myogenic differentiation (aka Triton tumor) appear similar but are notable for a neurofibroma-like or sarcomatous background.

Lipomatosis of nerve
Lipomatosis of nerve has many synonyms including lipofibromatous hamartoma, fibrolipomatous hamartoma, lipofibroma and fibrolipomatosis. Regardless of terminology, the lesion is usually solitary and occurs in adolescents or young adults and is twice as common in females. Patients present with a mass and sensorimotor deficits involving distal peripheral nerves of the upper extremities. True macrodactyly (enlargement of bone and soft tissue) is common. Histologic features are best accessed on nerve cross section which show the epineurium expanded by adipose tissue and to a lesser degree by fibrous tissue. Small branches of the nerve may also be involved. The nerve may show focal pseudo-onion bulb formation and
increased perineurial cells surrounding nerve fibers. However, the presence of fat distinguishes these lesions from intraneurial perineuriomas.

**Traumatic neuroma**

Traumatic neuromas occur at the site of partial or complete nerve transection and result from an ineffective attempt of the injured nerve to regenerate. The lesion results in a painful nodule in the area of previous injury. Most traumatic neuromas arise in the postsurgical setting, but in some instances, they follow insignificant injuries or may be present at birth. In utero examples occur after autoamputation of a supernumerary digit and appear as a small bump/rudimentary digit, often termed “rudimentary polydactyly”. Of note, the clinical practice of suture ligation with subsequent auto-amputation for polydactyly may also lead to painful neuromas at the site of the previous digit. Grossly the lesions are circumscribed nodular masses seen at the stump of a transected nerve or along the course of a crushed/incompletely transected nerve. Microscopically there is a disorganized proliferation of axons, Schwann cells and perineurial cells. A more organized “parent nerve” may be seen entering the neuroma, but the lesion itself is not well-organized. There is usually some degree of surrounding fibrosis. Inflammation and foreign body giant cell reaction may be seen as well. Since traumatic neuromas may be seen at virtually any anatomic site, the differential diagnosis is large. However, the history and evidence of previous injury aid in the exclusion of other entities.

**Localized interdigital neuritis (“Morton’s Neuroma”)**

Localized interdigital neuritis (LIN) is a localized, degenerative process most often seen in the plantar digital nerve. There is a strong female predilection and patients present with pain under the metatarsal arch between the third and fourth toes, which is exacerbated by exercise. Grossly, LIN is a small (<1cm), fusiform expansion of the nerve. The lesion is degenerative, not proliferative as in reactive/traumatic neuromas. Epineurial and perineurial tissue is fibrotic which may be highlight with trichrome staining. Surrounding vessels are hyalinized and thrombosis may be identified. Immunohistochemistry is generally not needed for diagnosis, but will highlight loss of axons and Schwann sheaths. There is little to no inflammatory infiltrate.

**Ganglion cyst of nerve**

Ganglion cysts occur adjacent to joints and are thought to arise from joint fluid dissecting through the associated nerve. There is a male predilection with the majority occurring in the common peroneal nerve near the head of the fibula. Cysts can cause nerve compression with associated sensorimotor defects. The cysts lack an epithelial lining and are filled with mucin and occasional histiocytes. The cyst wall becomes progressively fibrous with
surrounding distorted nerve fibers. While they are uniloculated cysts, they may have a tortuous path along the nerve so that they appear multiloculated on histologic sections. Ganglion cysts are rarely confused with other lesions. Vascular/lymphatic malformations can be excluded by the lack of endothelial lining and other peripheral nerve sheath lesions are excluded by the lack of S-100 and EMA staining.
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