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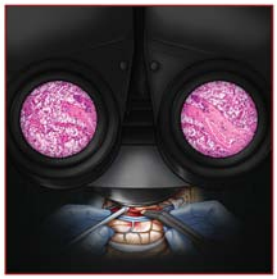

Diagnostic Pathology of Tumors of Peripheral Nerve

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Neoplasms of the peripheral nervous system represent a heterogenous group with a wide spectrum of morphological features and biological potential. They range from benign and curable by complete excision (schwannoma and soft tissue perineurioma) to benign but potentially aggressive at the local level (plexiform neurofibroma) to the highly malignant (malignant peripheral nerve sheath tumors [MPNST]). In this review, we discuss the diagnostic and pathologic features of common peripheral nerve sheath tumors, particularly those that may be encountered in the intracranial compartment or in the spine and paraspinal region. The discussion will cover schwannoma, neurofibroma, atypical neurofibromatous neoplasms of uncertain biological potential, intraneural and soft tissue perineurioma, hybrid nerve sheath tumors, MPNST, and the recently renamed enigmatic tumor, malignant melanotic nerve sheath tumor, formerly referred to as melanotic schwannoma. We also discuss the diagnostic relevance of these neoplasms to specific genetic and familial syndromes of nerve, including neurofibromatosis 1, neurofibromatosis 2, and schwannomatosis. In addition, we discuss updates in our understanding of the molecular alterations that represent key drivers of these neoplasms, including neurofibromatosis type 1 and type 2, *SMARCB1*, *LZTR1*, and *PRKAR1A* loss, as well as the acquisition of *CDKN2A/B* mutations and alterations in the polycomb repressor complex members (*SUZ12* and *EED*) in the malignant progression to MPNST. In summary, this review covers practical aspects of pathologic diagnosis with updates relevant to neurosurgical practice.

KEY WORDS: Neurofibroma, Schwannoma, MPNST, Neurofibromatosis, Schwannomatosis, Schwann cell, *NF1*, *NF2*, *SMARCB1*, *LZTR1*, *PRKAR1A*

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The peripheral nervous system is composed of peripheral nerves and ganglia, which arise from the brain stem or the spinal cord and course throughout the body to reach its various targets. Its function is to provide somatic and autonomic innervation. The peripheral nerves are formed by bundles of axons and are defined at the microscopic level by myelination mediated by Schwann cells. Peripheral nerves are composed of organized specialized tissue forming 3 layers: the endoneurium, the perineurium, and the epineurium (Figure 1). The anatomical distribution and histological complexity of the peripheral nervous system is reflected in the morphological and biological heterogeneity of the tumors that arise or differentiate toward its various cell components. Tumors of peripheral nerve range from benign to highly malignant.

Comprehensive molecular genetic profiling using high resolution platforms is currently transforming the approach to pathologic diagnosis of disease and cancer, including peripheral nerve sheath tumors (PNSTs). Well-defined morphological criteria still allow for classification in most cases, but global methylation profiling[1] in tumor and next-generation sequencing platforms in tumor and blood[2,3] may provide additional diagnostic and prognostic information. Although PNSTs usually develop sporadically in patients lacking a familial history or genetic predisposition, they are important components of a variety of genetic syndromes and pathologic characterization constitute important diagnostic criteria with consequences for clinical follow-up and genetic counseling. These syndromes mainly include

ABBREVIATIONS: ANNUBP, atypical neurofibromatous neoplasms of uncertain biological potential; **EBV,** epstein barr virus; **EMA,** epithelial membrane antigen; **GTP,** guanosine triphosphate; **HPFs,** high power fields; **MMNST,** malignant melanotic nerve sheath tumor; **NFP,** neurofilament protein; **PRC,** polycomb repressive complex

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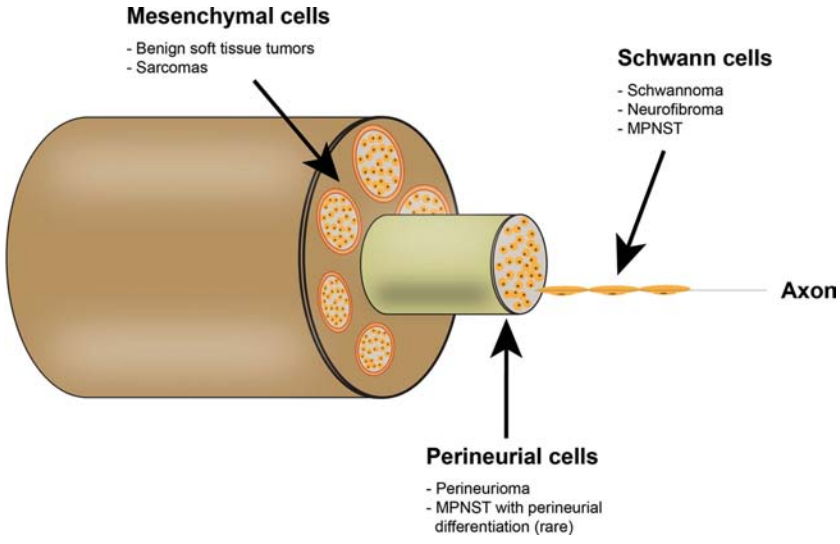

FIGURE 1. *Microanatomy of peripheral nerve. The peripheral nerve is composed of epineurium surrounding individual units (fascicles, in light green). The various nerve sheath tumors share phenotypic properties with the non-neoplastic cell components illustrated, predominantly with Schwann cells. Perineurial cells form the perineurium surrounding individual fascicles and have phenotypic overlap with the neoplastic cells of perineurioma. A variety of mesenchymal cells populate the epineurium, and although rare, there is a wide morphological and biological variation in the group of soft tissue neoplasms that may also involve the peripheral nerve as a primary site. Note that the phenotypic overlap of neoplasms with non-neoplastic cell counterparts does not imply that the latter are the cell of origin for the related neoplasms. In experimental models, cells of origin tend to be stem cell/progenitor cell precursors.*

neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), schwannomatosis, and Carney complex[4] (Figure 2).

In this review, we focus on the major categories of PNST that are likely to be encountered in neurosurgical practice. We focus on those that develop predominantly intracranially and in spinal nerve roots (Table). Key histologic and molecular genetic features that are useful for diagnosis are particularly emphasized.

SCHWANNOMA

Schwannomas are benign nerve sheath tumors composed of neoplastic Schwann cells. They develop at multiple body sites but intracranially they favor the vestibular branch of the VIII cranial nerve. On imaging, they present as masses of the cerebellopontine angle (Figure 3). As discussed below, bilateral vestibular schwannomas are diagnostic of NF2.[5] Schwannomas may also involve other cranial nerves and in rare occasions be entirely intraparenchymal within the brain.[6] Grossly, they are usually solitary, and the cut surfaces display a light-tan appearance surrounded by a fibrous capsule. A yellow color is frequent because of lipid content or lipid-laden macrophages. Variably sized cysts and hemorrhagic changes may be present. Histologically, in their classic form, schwannomas contain compact patterns (Antoni A), alternating with loose patterns (Antoni B). The Antoni A zones are characterized by increased cellularity and spindle nuclei. These zones are studded with clumps of cellular aggregates, where palisading patterns called Verocay bodies may be encountered, which are almost diagnostic at the histologic level (Figure 3). Paradoxically, Verocay bodies are frequently absent in vestibular schwannomas. The Antoni B zones are disorganized arrangements that are hypocellular and feature a variable macrophage infiltrate. The surrounding capsule is formed by multiple layers of collagen fibers. Other common histologic findings in schwannomas include hyalinized vessels with perivascular hemosiderin deposition, cystic spaces, and degenerative atypia ("ancient change"). Malignant transformation in schwannomas is exquisitely rare but usually takes the form of epithelioid malignant peripheral nerve sheath tumor (MPNST), a round cell malignancy or angiosarcoma.[7,8]

On immunohistochemistry, schwannomas are diffusely positive for mature Schwann cell markers, including S100 and SOX10 protein (Figure 3). Collagen IV and reticulin special stains are positive around individual cells. Epithelial membrane antigen (EMA) outlines perineurial cells peripherally but is negative in neoplastic cells. Neurofilament protein (NFP) highlights rare entrapped axons, but these are usually encountered in the periphery. Neoplastic cells in schwannoma also express vascular endothelial growth factor and antiangiogenic therapy with bevacizumab is often used for progressive vestibular schwannomas in NF2 patients.[9]

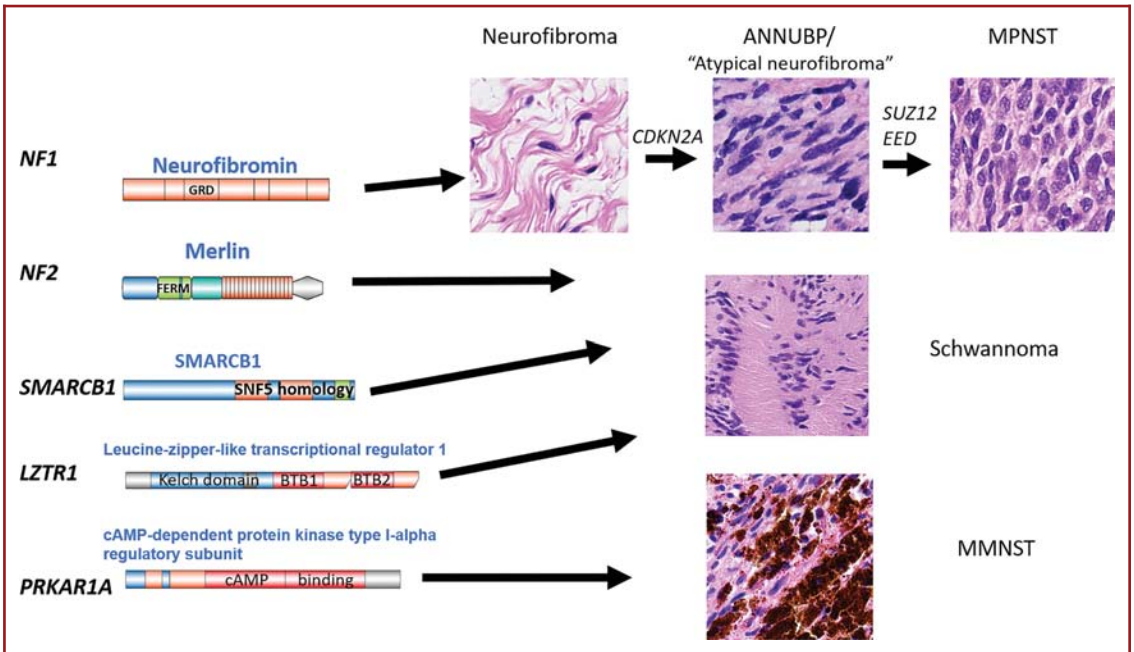

FIGURE 2. *Summary of molecular genetic pathogenesis of nerve sheath tumors. Tumor syndromes of nerve usually develop secondary to germline mutations in several key tumor suppressor genes: NF1, NF2, SMARCB1, or LZTR1 (schwannomatosis) and PRKAR1A (MMNST, in Carney complex). In the context of NF1, mutations associated with tumor progression include CDKN2A (p16) in atypical neurofibroma/ANNUBP and alterations in members of the PRC 2 (SUZ12 or EED).*

TABLE. Peripheral Nerve Tumors Relevant to Intracranial and Paraspinal Locations

Schwannoma
Neurofibroma
Perineurioma
Hybrid nerve sheath tumor
Schwannoma/perineurioma
Neurofibroma/schwannoma
Neurofibroma/perineurioma
ANNUBP
MMNST
MPNST
Miscellaneous
Lipoma of VIII cranial nerve
Glomus tumor of nerve
Sarcomas
Primary central nervous system tumors presenting in nerve root (myxopapillary ependymoma, hemangioblastoma)
Lymphoma
Metastatic carcinoma

Cellular Schwannoma

This type of schwannoma is composed almost entirely of Antoni A patterns lacking Verocay bodies (Figure 3). Although benign, it often displays local aggressiveness (eg, bone erosion). Dense cellularity and mitotic activity make this schwannoma variant particularly prone to be mistaken for malignancy.[10] Important typical features that help in avoiding this pitfall include the presence of a continuous peritumoral capsule, a rich macrophagic infiltrate, and the diffuse expression of Schwann cell markers (S100 and SOX10)[11] and, in contrast to most MPNST, retain H3K27 trimethylation (or H3K27me3).[12] A diffuse lymphocytic cuff under the capsule may be present, occasionally containing even well-formed lymphoid follicles. It must be highlighted that malignant transformation of schwannoma into MPNST is exquisitely rare and takes the form of a morphological change (eg, epithelioid, small cell, and angiosarcoma). Therefore, once the neoplasm is identified as a schwannoma, a simple increase in cellularity and/or mitotic activity, in the context of the features listed above, should not suggest malignant change. Cellular schwannomas may be encountered in a variety of body sites, including paravertebral areas. Involvement of the intracranial compartment is rare, but we have recently reported our experience with cellular schwannomas in this anatomic location.[13] The intracranial cellular schwannomas mostly developed in association with cranial nerve VIII or V. Local recurrences developed in a subset of patients, but no metastases or deaths were documented.

Plexiform Schwannoma

This schwannoma variant has a predilection for superficial sites, growing mostly in cutaneous or subcutaneous tissues, but

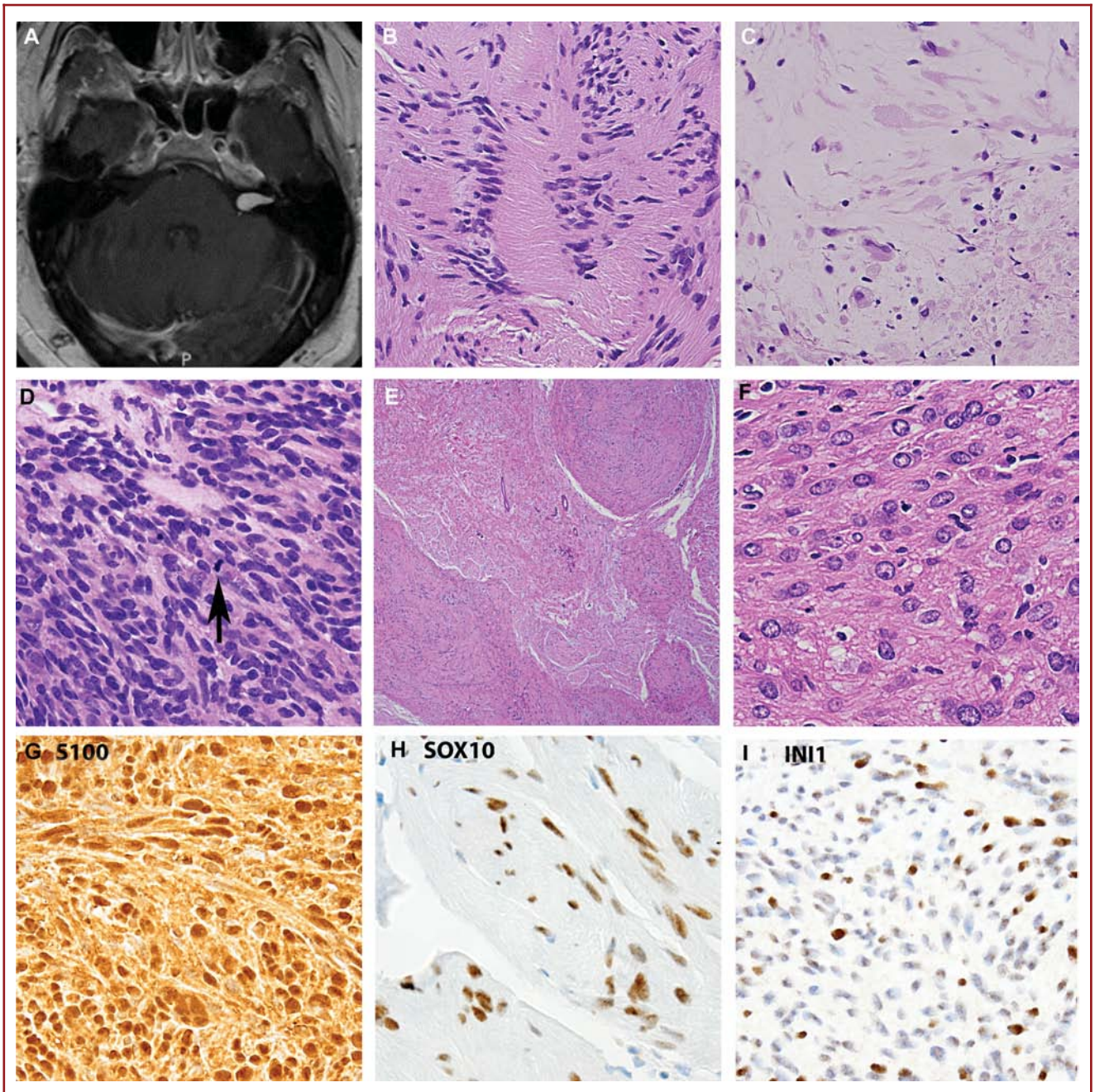

FIGURE 3. *Schwannoma.* **A**, *The vestibular branch of cranial nerve VIII is the main intracranial site of origin of schwannoma.* **B**, *Antoni A areas are compact and may contain characteristic palisades known as Verocay bodies.* **C**, *Antoni B patterns are composed of loose tissue with variable histiocytic infiltrates. Cellular schwannoma is a specific variant that is particularly prone to be mistaken for malignancy.* **D**, *Mitotic figures may be encountered (arrow).* **E**, *Plexiform neurofibromas are composed of multinodular aggregates of predominantly Antoni A tissue.* **F**, *Epithelioid schwannomas are rare, composed of plump cells with prominent nuclei and nucleoli. Strong expression of mature Schwann cell markers is typical of all schwannomas, including S100* **G** *and SOX10* **H**. **I**, *Patchy loss or a "mosaic" pattern of INI1/SMARCB1 immunostaining is typical of syndrome-associated (NF2 and schwannomatosis) schwannomas.*

may also develop in major peripheral nerves and plexi.[14] Their distinctive feature is a plexiform or nodular growth pattern (Figure 3). A capsule is usually absent. Plexiform schwannomas may be associated with local recurrences, but malignant transformation is exceedingly rare. Most occur sporadically, but a small subset (~5%) develops in genetic syndromes (NF2 or schwannomatosis). Other rare schwannoma variants include epithelioid,[15] neuroblastoma-like,[16] and reticular.[17]

Molecular Genetics

One important aspect of the diagnostic pathology of schwannomas is that when multiple, they are an important component of NF2 and schwannomatosis, and they represent important diagnostic criteria for these syndromes.[5,18] The hallmark of NF2 is the presence of bilateral vestibular schwannomas. Additionally, these patients develop other tumor types, particularly meningiomas and ependymomas. Approximately half of NF2 patients have a familial history. Schwannomatosis is sporadic in most instances (75%-85%), with approximately 15% to 25% being inherited. These patients almost exclusively develop schwannomas, but in rare instances, they also develop meningiomas.[19,20] Although schwannomas developing in genetic syndromes and sporadically are indistinguishable in most instances, features overrepresented in syndrome-associated cases, include whorling patterns, myxoid change, nerve edema/infiltration, and a mosaic pattern of SMARCB1/INI1 loss by immunohistochemistry.[21] The exception is NF2-associated vestibular schwannomas, where SMARCB1/INI1 positivity remains intact.[22]

A loss of function mutation in the *NF2* gene is the most common genetic feature of schwannomas in sporadic and familial forms. The *NF2* gene is located at the 22q12.2 chromosomal locus and encodes Merlin. Merlin is known to interact with cell junctional complexes and plays a role in contact-dependent inhibition. It has multiple additional cellular functions, including activation of oncogenic signaling pathways. Recent genetic profiling studies of schwannomas have also found recurrent mutations in *ARID1A*, *ARID1B*, and *DDR1* as well as a novel *SH3PXD2A-HTRA1* fusion in subsets of schwannoma.[23] Germline *NF2* mutations are diagnostic of NF2 syndrome. The germline alterations responsible for schwannomatosis are unknown in most instances, but *SMARCB1* (Chr 22q11.23 locus)[24] or *LZTR1* (Chr 22q11.21 locus)[25] germline mutations occur in subsets. SMARCB1 is a component of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling multiunit complexes that are Adenosine triphosphate dependent and mediate changes in chromatin architecture and gene expression. *LZTR1* encodes the *leucine zipper-like transcription regulator 1*, a member of the BTB-kelch superfamily. *LZTR1* is a Golgi complex protein and interacts with the CUL3-based ubiquitin ligase complex. In addition to schwannomatosis, this gene has also been found to be altered in Noonan syndrome and glioblastoma, and may participate in the regulation of RAS/MAPK signaling.[26]

Schwannomas developing in the context of SMARCB1-associated schwannomatosis represent an illustrative model on the cooperation of tumor suppressor loss in human neoplasia. In this context, the sequence involves a "four-hit" event in which sequential inactivation of both copies of *SMARCB1* and *NF2* occur in the individual tumors.[24] This event is probably facilitated by the localization of both genes in the chromosome 22q arm.

NEUROFIBROMA

Neurofibroma is another benign tumor composed of neoplastic Schwann cells, but unlike schwannoma, it also contains additional non-neoplastic components, including fibroblasts, mast cells, perineurial-like cells, and residual axons. Sporadic cutaneous neurofibroma is the most common subtype. However, multiple neurofibromas are a key feature of NF1, in which there may be involvement of multiple cutaneous sites, peripheral nerves, and spinal roots (Figure 4). Gross examination of neurofibromas involving peripheral nerves demonstrate fusiform enlargement of the parent nerve fascicle. Cut surfaces are variably yellow and translucent depending on the extent of myxoid stroma. The histologic features of neurofibroma are similar independent of specific subtype, and include a predominance of Schwann cells with thin wavy nuclei embedded in a myxoid matrix with variable amounts of collagen arranged in a haphazard fashion (Figure 4). Other cell components that are present in variable amounts include mast cells, lymphocytes, fibroblasts, and EMA-positive perineurial cells that all contribute to the tumor microenvironment. When involving nerve roots in the spine, neurofibromas may entrap ganglion cells through infiltration of sensory ganglia. In contrast to schwannoma, entrapped axons are frequent in the substance of the neoplasm because it is more infiltrative and, therefore, more challenging to resect without affecting the parent fascicle. The immunophenotype is characterized by uniform S100 and SOX10 expression in the neoplastic Schwann cells, whereas EMA labels perineurial cells and CD34 stromal cells. NFP typically outlines numerous entrapped axons.

Diffuse Neurofibroma

Diffuse neurofibromas typically form plaque-like enlargements of the skin and underlying subcutis. Approximately 10% of cases develop in NF1 patients. They lack a capsule and are poorly demarcated. These tumors may entrap adnexal and underlying soft tissue structures and frequently contain pseudomeissnerian corpuscles (spherical arrangements of S100-positive cell processes) (Figure 4). Transformation into MPNST in diffuse neurofibromas is rare, compared to plexiform and intraneural neurofibromas, but well documented.[27]

Plexiform Neurofibroma

Plexiform neurofibroma is a neurofibroma variant defined at the architectural level as involving multiple peripheral nerve fascicles, and therefore, it is frequently associated with larger

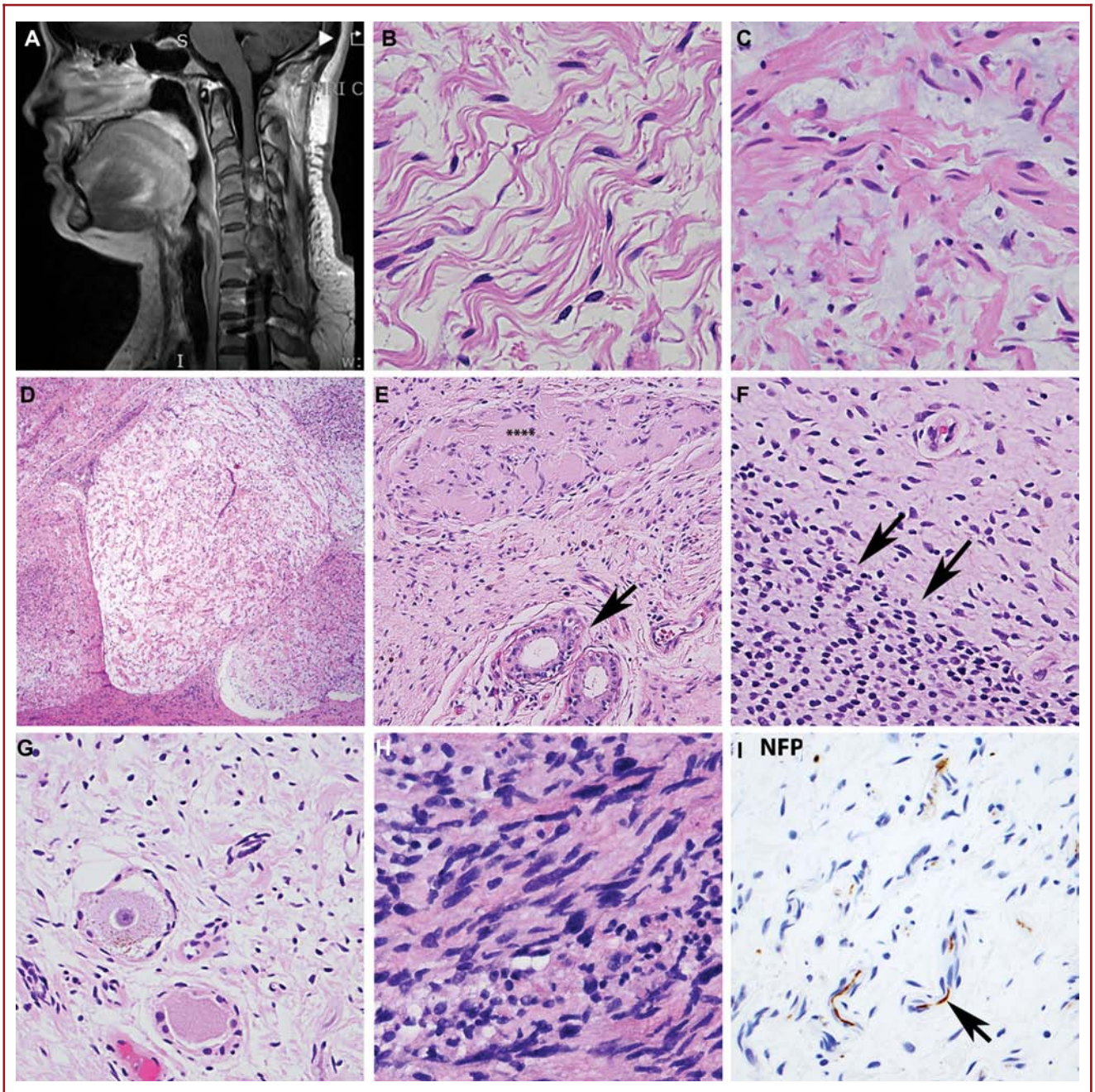

FIGURE 4. **A**, *Neurofibroma. Multiple neurofibromas involving cervical nerve roots in a patient with NF1. Neurofibromas are composed of wavy nuclei, somewhat smaller than those of schwannoma, with associated delicate collagen* **B** *and variable myxoid stroma* **C**. **D**, *Plexiform neurofibromas are typical NF1-associated tumors and form multiple tortuous nodules, reflecting multifasicular involvement best appreciated at low power.* **E**, *Diffuse neurofibromas may be infiltrating, frequently entrapping adnexal structures (arrow) and containing characteristic pseudomeissnerian corpuscles (asterisks). Massive soft tissue neurofibromas are typically enormous neoplasms, developing exclusively in NF1 patients.* **F**, *A cellular, but benign, round cell component is frequent (arrows).* **G**, *Neurofibromas frequently involve the dorsal roots in NF1 patients. Infiltration of dorsal root ganglia should not be mistaken for ganglion cell differentiation. The designation ANNUBP is usually reserved for the identification of some worrisome histologic features in small biopsies from NF1 patients but not meeting criteria for malignancy.* **H**, *This example demonstrates hypercellularity and nuclear enlargement.* **I**, *NFP immunostain is useful in highlighting underlying axons in the substance of neurofibromas (arrow).*

nerves and plexi. This subtype frequently affects (20%-50%) patients with NF1,[28] representing important clinical criteria for the diagnosis, and in these patients, it is an important precursor for MPNST.[29] In fact, plexiform neurofibromas involving large nerves and body regions are almost limited to patients satisfying clinical criteria for NF1. The rare cases lacking other clinical criteria for NF1 are usually classified as localized or "segmental" NF1. Malignant degeneration of plexiform neurofibromas occurs in approximately 5% of cases. In plexiform neurofibroma, the proliferation of Schwann cells involves multiple fascicles, englobing long nerve segments (Figure 4). Their distinctive feature is a multinodular enlargement, giving them the appearance of "bag of worms" or "string of onions." The histologic features are similar to neurofibromas occurring at other sites; therefore, the imaging, gross appearance, and low power histologic features are essential for diagnosis. Plexiform and diffuse components can co-exist in individual tumors.

Massive Soft Tissue Neurofibroma

This rare neurofibroma variant occurs exclusively in NF1 patients. These tumors are remarkable for their often-colossal size (which may span an entire limb) and the exquisite infiltration of local soft tissues, including skeletal muscle and even bone. They are characterized by slow progression, often beginning in childhood. They arise in subcutaneous tissue and may be covered by hyperpigmented skin.[30] Histologically, the tumors are characterized by extensive infiltration of underlying soft tissues, including skeletal muscle. Pseudomeisnerian corpuscles and cellular areas are frequently present (Figure 4).

Molecular Genetics

The defining genetic event for all neurofibroma subtypes is inactivation of the *NF1* gene (chromosome locus 17q11.2), encoding neurofibromin, a GTPase-activating protein that is expressed in many cell types in the central and peripheral nervous system. It regulates RAS signaling by mediating the conversion of Guanosine triphosphate (GTP)-bound RAS (active) to its Guanosine diphosphate (GDP)-bound state (inactive).[31-33] GTP-bound RAS results in activation of MAPK, extracellular signal-regulated kinase 1 and 2 (ERK1 and ERK2), and increased PI3K-mTOR signaling. The end result is increased transcription of target genes, cell growth, survival, and proliferation.[34-39] *NF1* inactivation also results in altered cAMP levels through regulation of adenylate cyclase, which affects non-neoplastic (eg, cognitive) as well as neoplastic manifestations of the disease. *NF1* gene inactivation is the sole recurring abnormality in neurofibromas,[40] with additional alterations acquired as part of atypical and malignant progression. Of therapeutic relevance, MEK inhibitors (eg, selumetinib) are currently feasible and may provide therapeutic benefit for some patients with plexiform neurofibroma.[41]

ATYPICAL NEUROFIBROMATOUS NEOPLASM OF UNCERTAIN BIOLOGICAL POTENTIAL

An atypical neurofibroma category has been controversial given the nosologic confusion that it creates and applied in various ways to denote a range of changes ranging from totally benign and clinically inconsequential (eg, degenerative atypia or "ancient change") to low-grade malignant change. Clear-cut diagnostic criteria for these important changes in the management of neurofibromas, particularly in the context of NF1, are lacking. A recent published consensus[42] proposed the designation of *atypical neurofibromatous neoplasms of uncertain biological potential* (*ANNUBP*) for a group of tumors with some worrisome histologic features, but not clearly deserving a diagnosis of malignancy (Figure 4). Criteria for the designation of ANNUBP include neurofibromas with at least 2 of the following 4 features: histologic atypia, loss of the typical neurofibroma architecture, hypercellularity, and increased mitotic activity (>1/50 but <3 mitotic figures per 10 High power fields (HPFs) or <1.5 mitoses/mm^2). This diagnosis should prompt additional evaluation (eg, tissue sampling) and close clinical follow-up. The sequence of molecular alterations responsible for malignant change in NF1-associated tumors is also beginning to be characterized, with premalignant change in neurofibroma demonstrating *NF1* inactivation, a low mutation burden, and *CDKN2A/B* loss.[43]

PERINEURIOMA

Perineuriomas are benign tumors composed of neoplastic perineurial cells. Two types of perineuriomas can be distinguished: intraneural and soft tissue perineuriomas, depending on their association to a major nerve or lack thereof, respectively. Historically, most cases of intraneural perineurioma were interpreted as localized hypertrophic neuropathy, which suggested a reactive process involving nerve and overlapping with a variety of reactive neuropathies. Immunohistochemical, ultrastructural, and molecular genetic studies have clarified intraneural perineurioma to be a neoplastic proliferation of perineurial cells rather than a reactive process. Macroscopically, intraneural perineuromas appear as segmental enlargements of nerve. Histologic examination demonstrates multiple concentric cytoplasmic layers forming whorls of variable size surrounding central axons ("pseudoonion bulbs")[44] (Figure 5). Despite the increased cellularity, mitotic activity is low to absent. Immunohistochemical features include membranous staining with EMA, GLUT-1, and Claudin-1 positivity, whereas S100 is negative, which differentiates neoplastic cells from underlying resident Schwann cells. Residual non-neoplastic Schwann cells and central axons in the pseudo-onion bulbs are identifiable with S100 and NFP immunoreactivity, respectively. At the molecular genetic level, most intraneural perineuriomas have *TRAF7* alterations, and a minority has NF2/chromosome 22 alterations.[45] Soft tissue perineuriomas share the same immunophenotype with

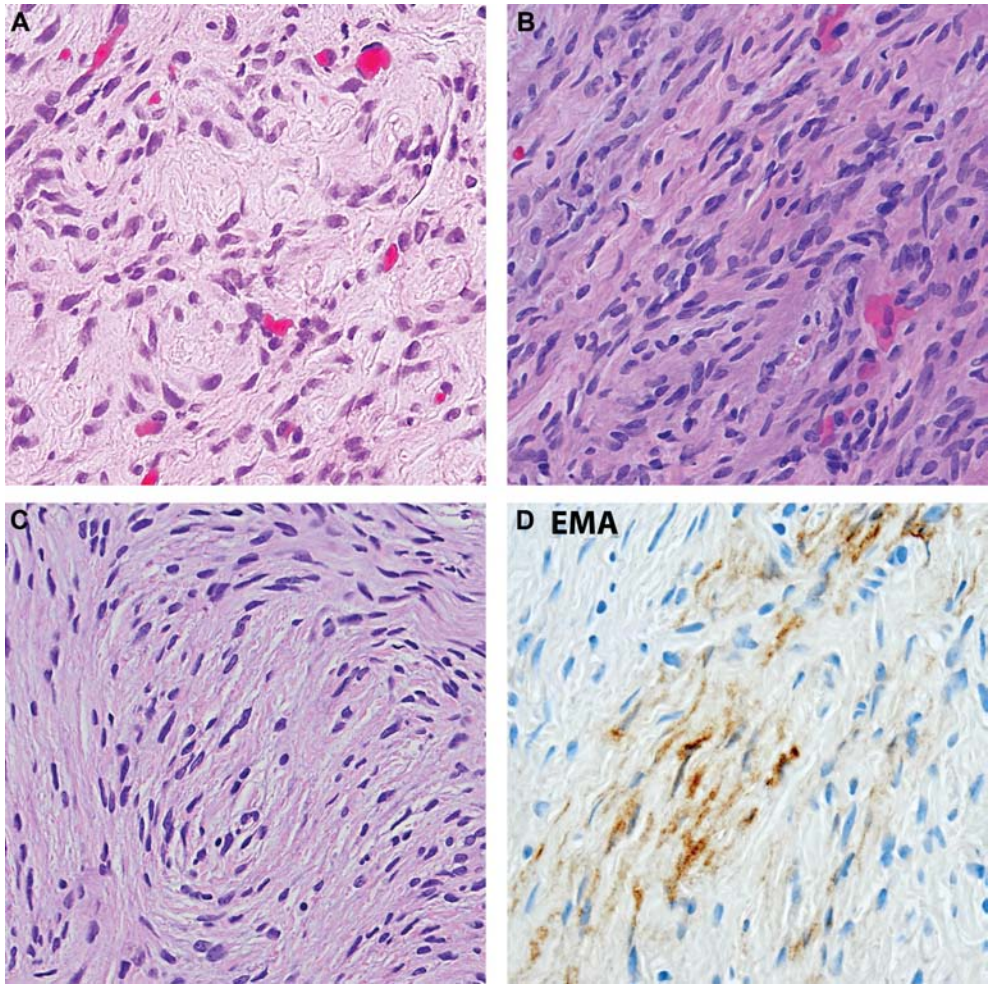

FIGURE 5. *Perineurioma.* **A**, *Intraneural perineurioma is a benign nerve sheath tumor characterized by the formation of pseudo-onion bulbs composed of neoplastic perineurial cells best appreciated on cross sections.* **B**, *Longitudinal sections may appear hypercellular, but the neoplasms are uniformly benign. Soft tissue perineuriomas form solid masses typically unassociated with major nerves.* **C**, *A storiform pattern is typical. EMA expression is typical of all perineurioma subtypes* **D**, *although it may be weak or focal.*

intraneural perineuriomas, but they form well-circumscribed masses unassociated with major nerves.[46] Molecular genetic alterations reported include deletions involving the *NF1* or *NF2* locus in a mutually exclusive fashion.[47] A few cases of intracranial perineuriomas have been reported, related to dura[48] or inside the ventricles.[49]

HYBRID NERVE SHEATH TUMORS

It has been increasingly recognized that a subset of benign nerve sheath tumors remains difficult to classify and place in one category because they have features of more than one recognized subtype (Figure 6). The most frequent variety is schwannoma/perineurioma, which more commonly occurs in the extremities in the form of subcutaneous/dermal masses. The neoplastic cells show a schwannian morphology, but the overall architecture resembles that of soft tissue perineuriomas. On immunohistochemistry, all tumors are positive for S100 and EMA.[50]

Another hybrid combination is neurofibroma/schwannoma, which may involve larger peripheral nerves, and appears to be overrepresented in patients with genetic syndromes (schwannomatosis, NF1, and NF2).[51] Monosomy 22 is frequent in these tumors.[52] Recently, recurrent *ERBB2* mutations were identified in a subset of hybrid neurofibroma/schwannomas developing in the context of schwannomatosis.[53]

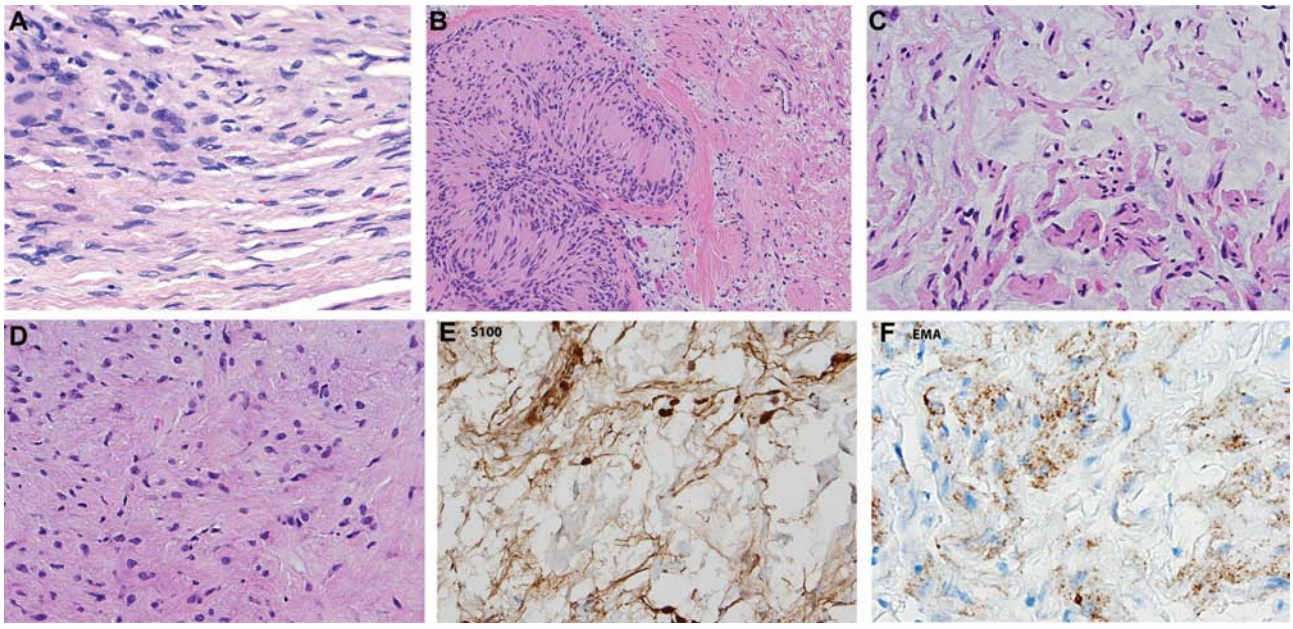

FIGURE 6. *Hybrid nerve sheath tumors. It is increasingly recognized that a subset of benign nerve sheath tumors may contain components of more than 1 tumor type.* **A**, *Hybrid schwannoma-perineurioma is the most frequent hybrid nerve sheath tumor.* **B**, *Schwannoma-neurofibroma usually takes the form of schwannian nodules (asterisk) in a plexiform neurofibroma background. Hybrid neurofibroma-perineurioma with neurofibroma* **C** *and perineurioma* **D** *components highlighted by S100* **E** *and EMA immunostains* **F**, *respectively.*

The least common variation is neurofibroma/perineurioma, the recognition of which is often done through immunohistochemistry, which highlights EMA-positive areas within a plexiform neurofibroma.[54]

MALIGNANT MELANOTIC NERVE SHEATH TUMOR

Malignant melanotic nerve sheath tumors (MMNSTs) are PNSTs composed of neoplastic Schwann cells with melanocytic differentiation. They present as solitary outgrowths bulging from spinal nerve roots and autonomic ganglia, and a subset is associated with Carney complex. On gross examination, MMNSTs form well-circumscribed, heavily pigmented tumors, with central necrosis and hemorrhage variably present. Histopathology shows a mix of spindled and epithelioid neoplastic cells arranged in fascicular patterns (Figure 7). Each neoplastic cell contains multiple intracytoplasmic brown inclusions corresponding to melanosomes. The nuclei are round and uniform with small nucleoli. A subset contains psammoma bodies, half of which have been associated with Carney complex in historic series,[55] but contemporary series have not found clinical differences between psammomatous and nonpsammomatous subtypes.[56] This syndrome is also characterized by endocrine hyperactivity, patchy skin hyperpigmentation, and a variety of tumor types, including cardiac myxomas. On immunohistochemistry, MMNSTs are positive for both Schwann cell and melanocytic markers, including S100, SOX10, melan-A, and HMB45. Collagen IV tends to outline tumor lobules. Molecular genetic studies of these tumors (sporadic and syndrome associated) have demonstrated frequent loss of function mutations in *PRKAR1A*[57] located on the chromosome locus 17p22-24. There is an additional, less-well-characterized locus on 2p16 that is responsible for a minority of Carney complex cases. Loss of the protein product of *PRKAR1A* can be detected through immunohistochemistry, which has diagnostic value. The mutations take the form of single base pair substitutions, deletions and insertions, or rearrangements.[58] PRKAR1A is one of the main regulatory subunits that form the Protein kinase A holoenzyme, and loss results in an increase in cAMP signaling.

The clinical course of MMNSTs historically has been hard to predict, and the tumors were formerly designated melanotic schwannoma, given the usual well-developed mature Schwann cell phenotype. However, Torres-Mora et al[56] reported high recurrence and metastatic rates in these tumors, justifying their reinterpretation as malignant neoplasms.

MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

MPNST are usually high-grade malignant spindle cell neoplasms arising in association with nerves, in pre-existing

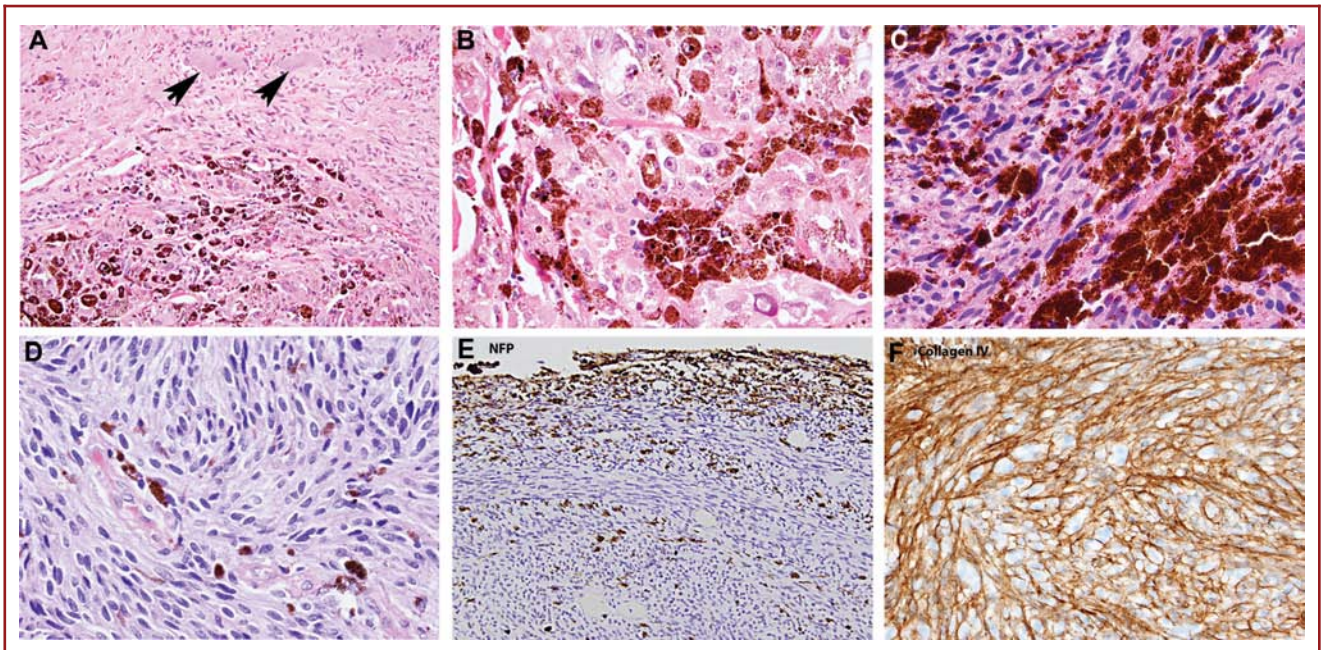

FIGURE 7. *MMNSTs.* **A**, *MMNSTs are distinctive nerve sheath neoplasms with conspicuous pigmentation that frequently involve nerve roots, ganglia (arrows indicating entrapped ganglion cells) and autonomic nerves. The tumors may be composed of epithelioid cells with macronucloli forming nests* **B** *or spindle cells* **C**. **D**, *Areas of decreased pigmentation may be encountered.* **E**, *NFP helps in outlining the axons in the presumed parent nerve.* **F**, *Collagen IV may be useful in outlining basal lamina deposition, a feature of Schwann cells.*

Schwann cell neoplasms (most frequently a plexiform neurofibroma) and/or demonstrating a variable Schwann cell phenotype (Figure 8). They are aggressive tumors characterized by a tendency to invade surrounding soft tissue and potential for hematogenous metastatic spread. MPNST can develop in association with NF1, after radiation exposure, or arise sporadically. Macroscopically, MPNST present as adherent, exophytic masses. They have a large variability in terms of size and consistency, ranging from microscopic change in a pre-existing neoplasm to massive tumors. Areas of necrosis and hemorrhage are common. Microscopically, they are usually cellular neoplasms composed of spindle-shaped cells with tapered nuclei. They frequently have alternating hyper- and hypocellular areas, which impart a marbled appearance at low power. Brisk mitotic activity and necrosis are frequent. Perivascular aggregates with herniation inside the vascular lumen are a characteristic feature. A small subset of MPNST is considered low grade, a designation usually applicable to areas of malignant change within plexiform neurofibromas in NF1.

Immunohistochemical stains demonstrate variable S100 and/or SOX10 expression, which is decreased in comparison with schwannomas, and maybe altogether negative.[11] MPNST also demonstrate loss of neurofibromin expression and H3K27 trimethylation. The latter is a key epigenetic marker that is lost in MPNST and has relatively high specificity for the diagnosis.[12] However, close mimickers such as melanoma may also demonstrate loss.[59]

As mentioned above, most MPNST are high grade and easily recognized as malignant at the histologic level. The diagnosis of low grade MPNST is usually made in the context of NF1-associated neurofibromas with areas of ANNUBP transitioning to low grade MPNST. Although difficult to define, proposed criteria include the presence of changes typical of ANNUBP but, in addition, greater increases in mitotic activity (1.5-4.5 mitoses/mm^2) or 3 to 9 mitotic figures per 10 HPFs and no necrosis.[60] High-grade MPNST are characterized by increased mitotic activity, and necrosis is frequent.

MPNST typically develop in association with larger nerves and plexiform neurofibromas. Rarely they may develop in association with cranial nerves and/or in the intracranial compartment.[61] In a series of 17 cases, the vestibular nerves were most commonly involved, and the tumors were aggressive as those occurring in other sites. Careful consideration must be given to exclusion of desmoplastic/spindle cell melanoma, a more common diagnosis in head and neck sites.

The morphological spectrum of MPNST is remarkable. Heterologous differentiation may present with a variety of morphologies, including cartilage, bone, skeletal, and smooth muscle. Glandular differentiation is a rare but well documented phenomenon. Other MPNST variants include epithelioid MPNST and MPNST with perineurial differentiation.

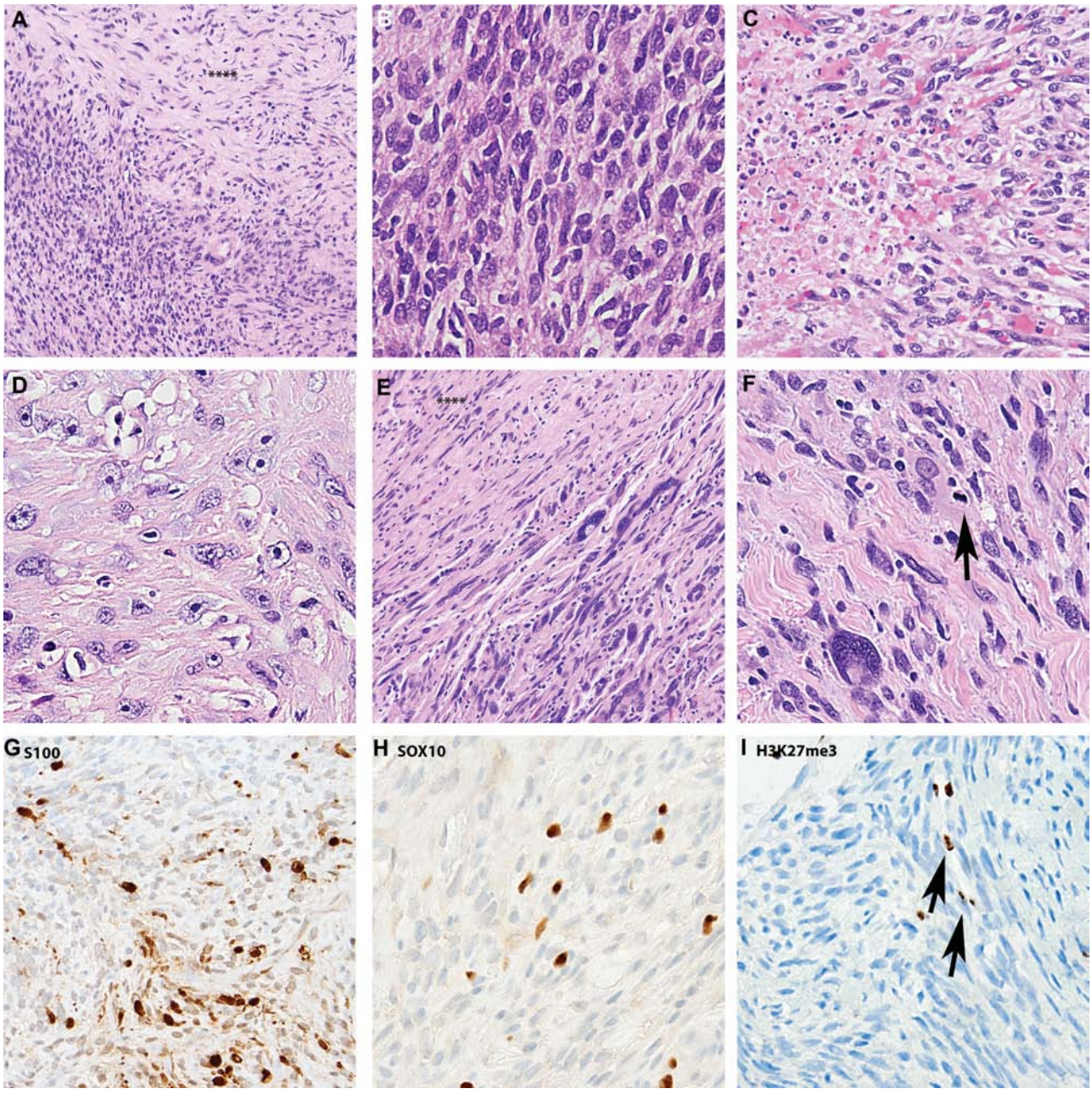

FIGURE 8. *MPNSTs. MPNST are usually high-grade neoplasms that may arise in a neurofibroma precursor (asterisks)* **A** *and are characterized by hypercellularity/nuclear atypia* **B** *and frequent necrosis* **C**. **D**, *Epithelioid MPNST is a distinctive subset characterized by neoplastic cells with large nuclei with macronucleoli. MPNST developing in a pre-existing neurofibroma (asterisks)* **E** *and displaying low-grade histology, including lesser cell density and rare mitotic figures (arrow)* **F**. *MPNSTs typically have decreased expression of mature Schwann cell markers, including S100* **G** *and SOX10* **H**, *and in fact may be completely negative. Loss of H3K27 trimethylation (H3K27me3) is a relatively specific feature.* **I**, *Retained positivity in underlying endothelial cells is a useful internal positive control (arrows).*

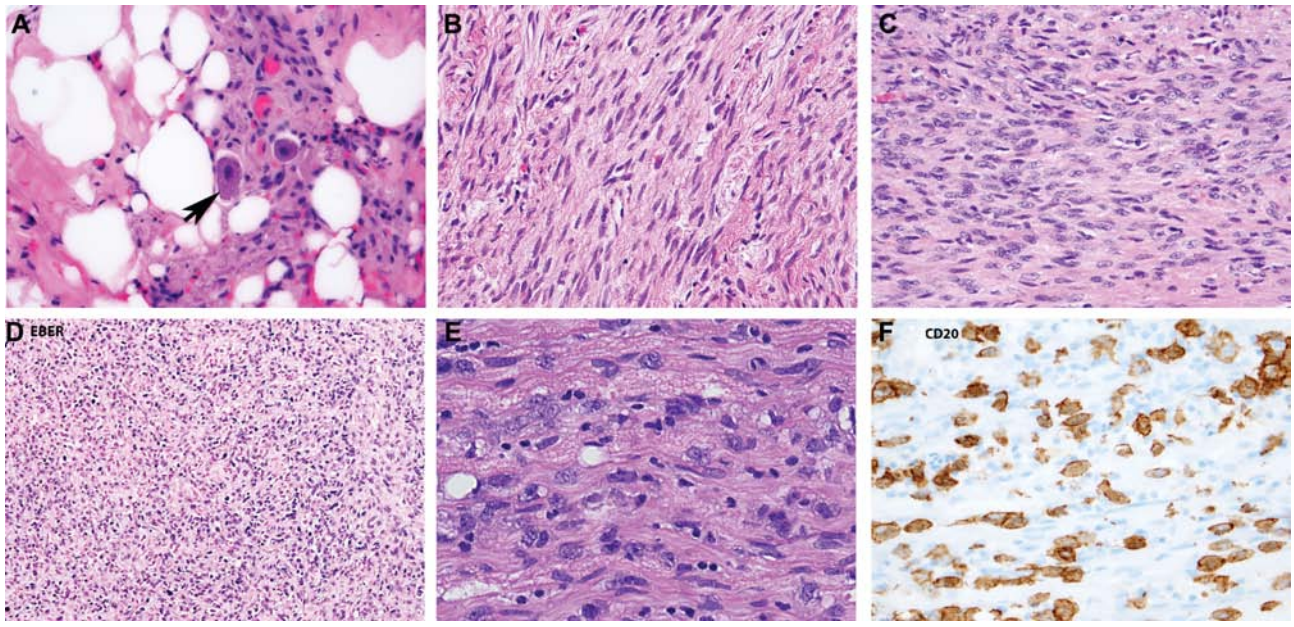

FIGURE 9. *Miscellaneous tumors of peripheral nerve. A variety of soft tissue neoplasms may develop in association with a major nerve or nerve root.* **A**, *Lipoma of cranial nerve VIII with associated entrapped ganglion cells (arrow). Synovial sarcoma is a malignant difficult mimic of nerve sheath tumors when arising primarily in nerve.* **B**, *The distinction may require molecular testing.* **C**, *Smooth muscle tumors may also involve peripheral nerve occasionally.* **D**, *This example developed in an immunosuppressed patient and was EBV associated (in Situ hybridization study for EBV encoded ribonucleic acid). Diffuse large B-cell lymphoma may present as a peripheral nerve infiltrate overriding axons* **E**, *and is typically outlined by CD20 immunostain* **F**.

Molecular Genetics

In MPNST germline or acquired *NF1*, inactivation is considered an important initiating event, which is followed by a cascade of other mutations that contribute to the malignant phenotype.

CDKN2A inactivation and somatic mutations in members of the polycomb repressive complex (PRC) *SUZ12* and/or *EED* are additional important events.[62,63] The mutations in PRC components lead to loss of H3K27 trimethylation, which is more typical of high-grade tumors.

MISCELLANEOUS

A variety of benign and malignant neoplasms may involve peripheral nerves, both intracranially and at spinal/perispinal sites. They vary from rare (lipoma) to relatively more frequent (metastatic carcinoma/melanoma).

Lipoma of the 8th cranial nerve is a unique benign lesion that differs from lipomas arising at other anatomic locations. Magnetic resonance imaging studies are excellent at preoperative diagnosis given the fatty content, which results in hypersensitivity on postcontrast T1-weighted images, disappearing on fat suppression. These lesions are composed predominantly of fat (Figure 9), but other mesenchymal components may be encountered such as smooth or skeletal muscle.

Myxopapillary ependymoma, hemangioblastoma, and paraganglioma are usually considered tumors of the central nervous system, but they can present as purely involving the spinal nerve roots. A variety of sarcomas may involve the paraspinal region, nerve roots, and major nerves and are important tumors in the differential diagnosis of MPNST. Leiomyosarcoma may have morphological overlap with MPNST and may also express S100. However, immunohistochemical markers of smooth muscle are consistently present, such as smooth muscle actin and desmin. A group of smooth muscle tumors that may also involve the intracranial compartment and spinal nerve roots in immunosuppressed patients are the Epstein Barr Virus (EBV)-related smooth muscle tumors (Figure 9). Monophasic synovial sarcoma is a more troublesome mimic of MPNST and may present as a purely intraneural mass[64] (Figure 9). Cytokeratin and EMA are typically positive, but they may also express S100 and SOX10. Neurofibromin and H3K27 trimethylation immunoreactivity are usually retained.[12,65-68] The identification of SSX1/SSX2 gene fusions are diagnostic.[69]

Melanoma, particularly the desmoplastic variant, may be difficult to distinguish from nerve sheath tumors, and it may be a mimic of both neurofibroma and MPNST. Prominent neural infiltration ("neurotropic melanoma") is a well-described phenomenon, and may in fact be more frequent in head and neck sites than MPNST. Lymphoma, usually the diffuse large

B-cell type, can present with prominent peripheral nerve or nerve root infiltration (Figure 9). Carcinoma from a primary site may also involve cranial or spinal nerves by direct spread from head and neck sites (eg, squamous cell carcinoma and adenoid cystic carcinoma) or pelvis (eg, prostatic adenocarcinoma) all the way up to their point of origin, in addition to involving nerve as metastatic deposits.

CONCLUSION

The spectrum of neoplasms that may involve the peripheral nervous system is wide, but most primary tumors have a Schwann cell phenotype, at least in part. They range from the most benign to the most malignant tumors encountered in surgical pathology. They also illustrate the value of diagnostic precision in their pathologic evaluation, even when benign, given their solid place in the diagnostic criteria of importance to the management of patients with genetic syndromes.

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