

Neuroscience II

Pathology of peripheral nervous tissue tumor

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SCHWANNOMA

Clinical Features

Schwannomas account for 8% of intracranial tumors, 85% of cerebellopontine angle masses, and almost one-third of spinal nerve root tumor. When symptoms occur, there are usually associated with corresponding cranial neuropathy or spinal radiculopathy, most likely sensory in nature.

Approximately 90% are sporadic and solitary while 4% occur in patients with neurofibromatosis type 2 (NF2). A roughly equal percentage may be multiple but are unassociated with NF2. They occur most frequently in mid-adulthood with spinal examples more common in women. Intraparenchymal cerebral schwannomas are associated with a younger age and male predominance. Schwannomas are assigned to WHO Grade I.

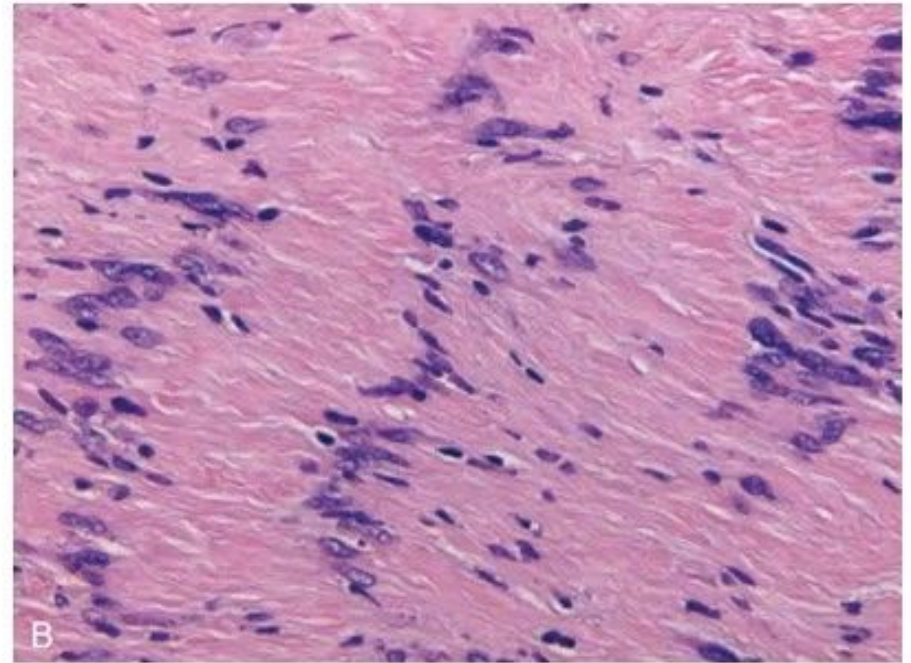
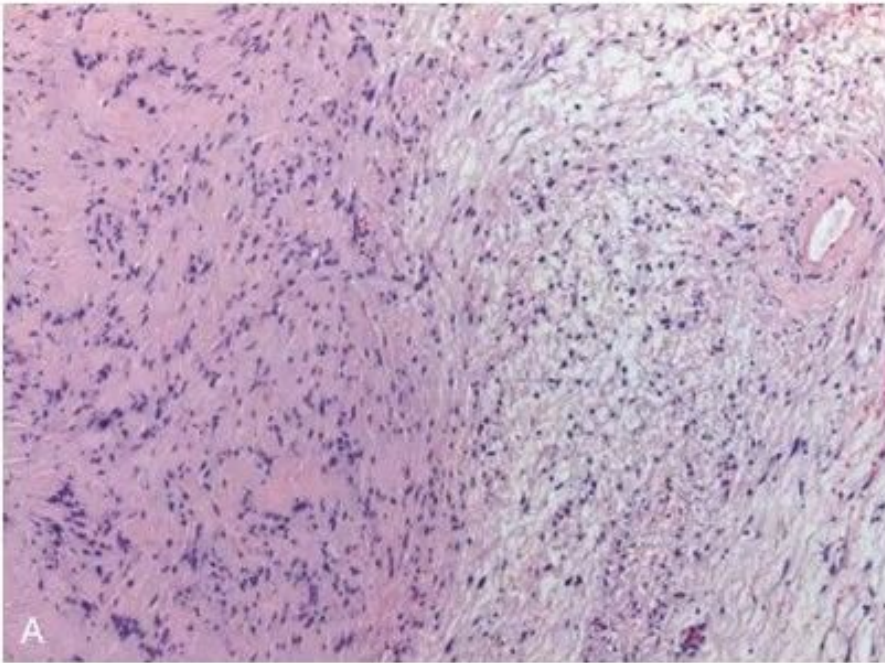


Most intracranial schwannomas arise in association with the eighth cranial nerve in the cerebellopontine angle. Bilateral examples are considered diagnostic of NF2. They are otherwise preferentially located in sensory rather than motor cranial nerves as well as in spinal sensory nerve roots.

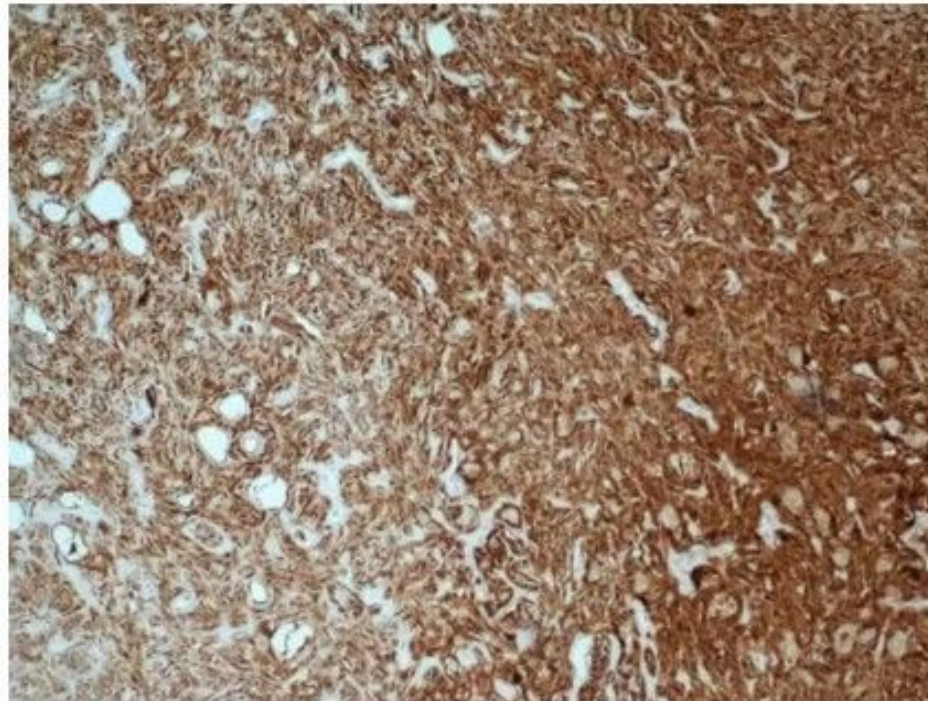


Pathology

Schwannomas in all locations share a variety of histologic appearances, dominated by spindle cells forming two basic patterns: compact elongated cells with occasional nuclear palisading or Verocay bodies (Antoni A pattern) and a looser pattern with indistinct cell processes and delicate vacuolation.



Schwannoma cells should be strongly and diffusely immunopositive for S-100 protein, may express Leu-7 and calretinin, and may focally express GFAP. Intralesional axons may be detected in small numbers by neurofilament immunohistochemistry, particularly in NF2 or schwannomatosis-associated tumors



Cellular Schwannoma

The presence of predominantly Antoni A tissue and the nuclear zones of Verocay bodies yields a hypercellular appearance to this variant . They are more common in paravertebral locations in the pelvis, retroperitoneum, and mediastinum , although cranial nerves may be involved. Mitotic activity, although more common than in conventional schwannomas, is usually less than four per ten high-powered fields and should not be confused with the usually higher proliferative index seen in malignant peripheral nerve sheath tumors. Flow cytometry may show abnormalities in ploidy .In spite of these abnormalities, cellular schwannomas should be considered more closely related to conventional schwannomas as no metastatic examples have been recorded and they almost never undergo malignant transformation.



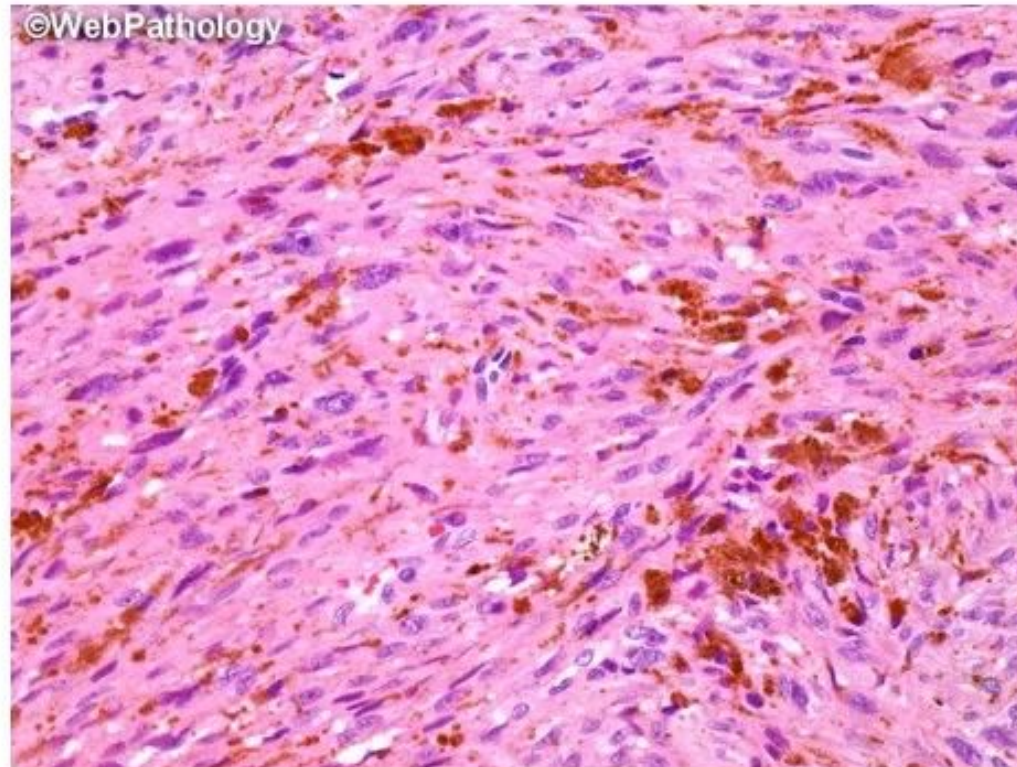
Plexiform Schwannoma

These are most frequently encountered as a skin or subcutaneous tumor of an extremity, heads and neck, or trunk. They are not associated with NF1, have a low association with NF2, and have also been noted in non-NF2 patients with multiple schwannomas (schwannomatosis). They are defined as schwannomas growing in a plexiform or multinodular manner, either with conventional or cellular histological features .



Melanotic Schwannoma

Schwannomas are rarely grossly pigmented and are composed of cells having the ultrastructure and immunophenotype of Schwann cells but containing macronucleoli. Bleaching of the tissue section prior to immunohistochemistry may be required in order to plainly reveal the immunophenotype.



NEUROFIBROMA

Clinical Features

Neurofibromas are composed of a mixture of three cell types, including Schwann cells, perineurial like cells, and fibroblasts. They may be multiple and present as a plexiform subtype in association with NF1; however, neurofibromas occur most commonly as sporadic solitary nodules.

Neurofibromas correspond to WHO Grade I. Neurofibromas occur most commonly as a painless subcutaneous nodule or circumscribed mass involving a peripheral nerve. They are seen as neurosurgical specimens when involving spinal roots but are essentially unknown in cranial nerves



Pathology

Grossly, cutaneous neurofibromas are nodular or polypoid relatively well circumscribed masses involving skin and subcutaneous tissue. Peripheral nerve neurofibromas are well-circumscribed fusiform masses. Plexiform neurofibromas are traditionally determined by gross diagnosis, appearing as a multinodular mass composed of a tangle of wormlike cords. Neurofibromas exhibit a wide range of microscopic appearances; however, they tend to include areas composed of well-spaced spindle cells with ovoid or elongated nuclei and poorly defined cytoplasm. There may be a variable matrix of collagen, sometimes showing a fragmented appearance reminiscent of “shredded carrots”. Mast cells are a regular feature. There may also be scattered lymphocytic infiltrates. Some examples contain discrete parallel arrays of spindle cells reminiscent of pressure receptors, referred to as pseudo-Meissnerian corpuscles. Others may show conspicuous and multiple aggregates of spindle cells showing Schwannian



differentiation, thus allowing the diagnosis of neurofibroma with schwannomalike nodules. Neurofibromas may contain numerous atypical nuclei, termed atypical neurofibroma, or increased cellularity (cellular neurofibroma) although without significant increase in mitotic activity. Neither of these subtypes has been shown to carry a worse prognosis. Immunohistochemistry may reveal that only a subset of cells is S-100 protein positive. CD34 may also be detected. The notion that the presence of neurofilament-positive fibers within a neurofibroma may help to distinguish them from schwannomas has been challenged, whereby these may be found in both examples .



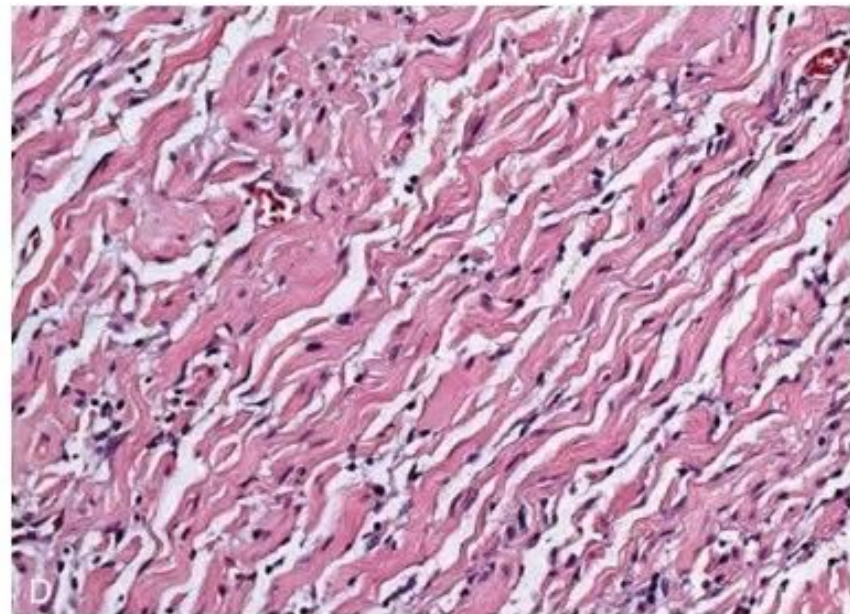
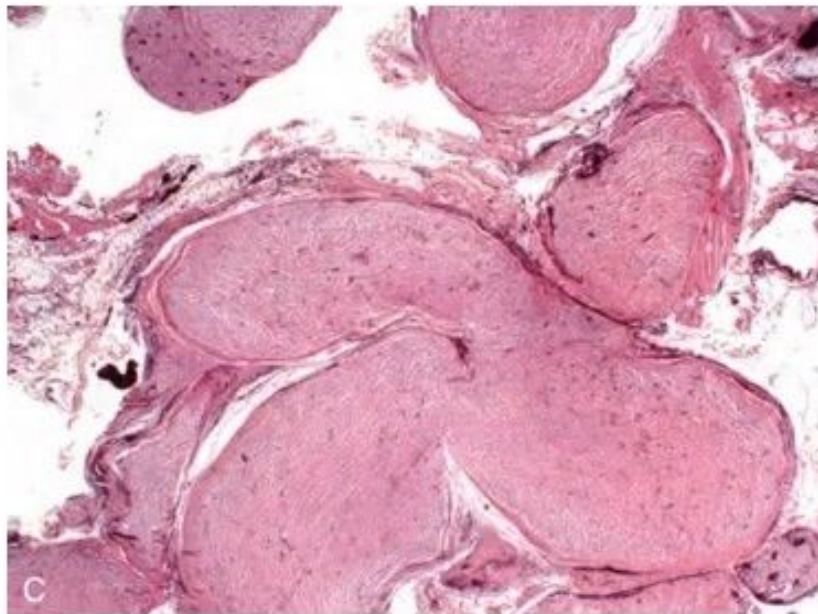
Plexiform Neurofibroma

Clinical Features

This is an uncommon but highly characteristic type of neurofibroma that preferentially involves large nerves. It occurs exclusively in NF1, although there is some debate over this point since rare examples have been reported in patients lacking other manifestations of NF1. Plexiform neurofibromas have a propensity for malignant transformation, estimated to be approximately 10% over a lifetime. They may develop during the first 1 or 2 years of life as a single subcutaneous swelling with ill-defined margins. Later in life, they may cause a severe disfigurement, sometimes being even life-threatening when occurring in the head or neck region.



Pathology These tangled, wormlike masses tend to reflect the degree of complexity in parent nerves such that highly branched nerves exemplified by paraspinal plexuses or number of fascicles in large caliber nerves like the sciatic results in the greatest degree of complexity. The mucin-rich stroma creates a glistening or translucent quality to the cut surface. The microscopic appearance of plexiform neurofibromas does not differ significantly from ordinary neurofibromas although the low-power examination will often highlight the curled and intersecting tumorous nerve bundles.



PERINEURIOMA

Clinical Features

There are two types of perineurioma: intraneural and soft tissue. Both types are associated with monosomy of chromosome 22. Intraneural perineuriomas were previously considered a form of hypertrophic neuropathy but are now recognized as an unusual cause of peripheral nerve sheath enlargement. Intraneural perineuriomas present in adolescents or early adulthood and cause progressive muscle weakness with variable muscle atrophy. Peripheral nerves and the extremities are more frequently involved although cranial nerve lesions have been rarely reported.



Soft tissue perineuriomas are not associated with nerves and are also quite rare. They occur predominately in the adult females with local mass effect within deep soft tissues. The general prognosis is favorable for perineuriomas, although rare instances of malignant transformation have been reported . Malignant perineuriomas arising in the soft tissue are usually not associated with a peripheral nerve.



Pathology

Intraneural perineuriomas cause a segmental enlargement of the affected nerves by a tubular or fusiform mass resulting in significant enlargement. Microscopically, they are formed by neoplastic perineurial cells proliferating throughout the nerve, forming concentric layers or whorls the around nerve fibers known as pseudo-onion bulbs, and forming vague fascicles. The proliferative process may extend into the perineurium. Axonal stains may show one or more axons at the center of the pseudo-onion bulb. Extensive hyalinization may also occur. Soft tissue perineuriomas are composed of wavy spindle cells with thin cytoplasmic processes in layers and embedded in whorls of collagen fibers



A storiform pattern may be recognized. Mitotic figures are usually scant. “Degenerative atypia” represented by pleomorphic or hyperchromatic nuclei and nuclear cytoplasmic inclusions may be seen in tumors of long duration. There may be extensive collagenous change, noted in examples occurring in the fingers of young males. Malignant soft tissue perineuriomas show invasive growth characterized by hypercellularity, hyperchromasia, and sometimes brisk mitotic activity, resulting in WHO grade II and if variable necrosis is noted, warrants a WHO grade of III. The hallmark of perineuriomas is the characteristic immunoreactivity for EMA in both normal and neoplastic perineurial cells. Other components of the lesion may be delineated such as Schwann cells by S-100 immunostaining and axons by neurofilament or silver impregnation techniques.



MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Clinical Features

Malignant peripheral nerve sheath tumors (MPNSTs) affect young and middle-aged adults with a slight female predominance. Pediatric examples account for 13% of cases in one series . NF1 is associated with between 50% and 60% of MPNSTs. Ionizing radiation, either therapeutic or through occupational exposure, may contribute to the development of a MPNST.

MPNSTs are usually found in large- and medium-sized nervous of the buttock with the sciatic nerve being the most frequently affected, and in addition the thigh, brachial plexus, upper arm, and paraspinal nerves



Wide resection is the treatment of choice with postoperative radiation therapy. Recurrence depends upon the extent of surgical resection. In the lower extremity and buttock, 40% may recur whereas over two-thirds recur in paraspinal locations. There is an overall metastatic rate of approximately 30–40% but is high as 65%, particularly in lesions arising in the lower extremity or buttock . Mortality from tumor is found in approximately two-thirds of patients and the presence of tumor at the resection margin figure greatly in predicting local recurrence and thus survival.



Pathology

The gross appearance of an MPNST may suggest that it has arisen in a large nerve in either a solitary or plexiform neurofibroma. They are globoid or fusiform and surrounded by a fibrous pseudocapsule of varying thickness. They display a firm opaque consistency on cut section with areas of necrosis grossly recognizable in the majority of cases. Pathologic sampling under ideal circumstances should allow for revealing the associated nerve or neurofibroma and the specimen should be treated with the goal of identifying resection margins.



MPNSTs show a wide diversity of histologic appearances as well as features that allow for grading. Generally speaking, they show features of a malignant spindle cell tumor composed of tightly packed cells with variable amounts of eosinophilic cytoplasm. Nuclei are elongated but in contrast to “benign” nerve sheath tumors, the nuclei are enlarged, hyperchromatic, and crowded. These findings may be especially useful in distinguishing a low grade MPNST from a cellular neurofibroma .It should be noted that finding of some mitotic activity may not be a reliable observation in distinguishing MPNST from lower grade tumors although the majority of MPNSTs exhibit a high mitotic index . In certain instances, it is possible to recognize a malignant transition from prior surgical resections or in the primary lesion of a transformation from a benign nerve sheath tumor such as neurofibroma, or ganglioneuroma/ganglioneuroblastoma to MPNST.



MPNST with mesenchymal differentiation include the so-called malignant Triton tumor, defined as MPNST with rhabdomyosarcomatous differentiation. It is estimated that 60% of patients with malignant Triton tumor have NF1.



TRAUMATIC NEUROMA

Clinical Features

Common clinical circumstances producing traumatic neuromas include brachial plexus avulsion injury from shoulder dystocia occurring in some vaginal deliveries, and other forms of either complete transection or crush injury of nerves, sometimes postsurgically or after seemingly insignificant trauma.

Pathology

These appear grossly as the firm nodular masses with an associated nerve. Histologic preparations will often reveal a transition from a relatively intact nerve to the neuromatous component, which is composed of small nodules of proliferating Schwann cells in a collagenous matrix . Close inspection will reveal bundles of regenerating axons within the Schwannian nodules. The stroma may be mucinous. The scarring reaction may include regional adipose or skeletal muscle tissue

