Clinical Application of Pathology

BRAIN TUMOURS VII – Primary Peripheral Nerve Sheath Tumours (PNST): Cranial, spinal & peripheral nerves

System: Nervous

Causes: Cancer

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Monday, January 09, 2017
**Anatomical background**: nerves consist of axonal processes (neurites) arising from centrally or peripherally located neurons and an investing supportive sheath consisting of Schwann cells and three layers; the epineurium, the perineurium and the endoneurium.

Axons are coated by a continuous single file of Schwann cells. The Schwann cells are connected by cell junctions and each is lined by a continuous external lamina. Their processes fold around an axon. The Schwann cells may form myelin.

Nerve fibres are thus an axon-Schwann cell complex and travel within the endoneurium which is a collection of fibroblasts and collagen fibres embedded in an acid mucopolysaccharide matrix. There are also small blood vessels but no lymphatics.

The **endoneurium** is encased in the loosely attached perineurium. The perineurium acts as a diffusion barrier protecting the endoneurium and its contents and is in direct communication with the arachnoid membrane.

The **perineurium** cells have elongated nuclei and long curved cell processes, complete with pinocytotic vesicles and inter-connecting tight cell junctions. The cells are arranged in one or more circumferential sleeves, each only one cell thick. The perineural cell sleeves themselves are separated by external lamina thicker than that lining Schwann cells and also by collagen fibrils.

External lamina lines the boundaries with endoneurium and epineurium as well.

The part of the nerve outlined by and including the perineurium is called a **nerve fascicle**, one or more of which form the cranial, spinal or peripheral nerves.

Nerve fascicles are separated, encased and bound together by a continuous fibrovascular layer called the **epineurium**. This is usually able to be distinguished from the adjacent soft tissues.

Vascular supply to the nerve is abundant and forms longitudinally oriented channels along the nerve.

**SCHWANNOMA – (neurilemoma, neurinoma))- 9560/0 - WHO grade I**

**Definition**: A schwannoma is a benign nerve sheath tumour composed of differentiated Schwann cells, which normally produce the insulating myelin sheath covering peripheral nerves.

**Sites**: commonest – cutaneous tissues of the head and neck, flexor surfaces of the extremities (especially peroneal and ulnar nerves), posterior mediastinum and retroperitoneum. Have a predilection to involve sensory nerves. Very common is a schwannoma of the vestibular component of the 8th cranial nerve.

**Incidence**: Schwannomas of the head and neck are a fairly common occurrence and can be found incidentally in 3–4% of patients at autopsy. Accounts for 5% of all benign soft tissue tumours.

**Age**: most common between 20 – 50 years.

**Gender**: equal in the sexes.

**Clinical presentation**: patient presents with a painless lump (unless it is a large mass) without neurological symptoms.

**Associated conditions**: Sporadic in 90%. However, 5% are plexiform or multiple, and are rarely associated with von Recklinghausen’s disease. 3% occur with neurofibromatosis type 2 (NF2), 2% with schwannomatosis (NF3) and 5% with multiple meningiomas with or without NF2.
Pathogenesis: schwannomas are derived from the myelinating cell of the peripheral nervous system and are composed almost entirely of Schwann cells. Are slow growing and mostly benign. 1% become malignant, degenerating into neurofibrosarcoma. Schwannomas typically grow within a capsule that remains peripherally attached to the parent nerve, so surgical removal is often successful. Most commonly, schwannomas impact the central nervous system (CNS) by involving the vestibular branch of cranial nerve VIII or the dorsal roots of the spinal cord.


The tumour (T) originates within a Schwann cell cylinder that surrounds an axon. The tumour subsequently grows, eccentrically compressing the normal adjacent axons. Schwann cell cylinders surrounding axons (light brown), endoneurium (dark yellow), and perineurium (tan and dark brown).

Schwannomas are homogeneous tumours, consisting only of Schwann cells. The tumour cells always stay on the outside of the nerve, but the tumour itself may either push the nerve aside and/or up against a bony structure possibly causing damage to the nerve. Drawing courtesy of Dr Aleta Ann Frazier and AIRP from Kransdorf MJ and Murphy MD. Imaging of soft tissue tumours.

Legend for diagram: Image on the left is a Schwannoma. The closed arrows are the entering and exiting nerve with the Schwannoma (S) within the epineurium – open arrows – but quite separable from the uninvolved native nerve N. The image on the right is a neurofibroma showing the tumour and the native nerve to be unable to be separated - asterisk. Entering and exiting nerve is centrally located relative to the mass – white arrows.


A. The yellowish tan gross specimen exhibits a thin capsule.

B. Cut section of the tumour reveals a uniform, solid parenchyma. Architecture of schwannomas may vary and also exhibit cystic or nodular consistency.
Another example – below - of a schwannoma demonstrating a well circumscribed and encapsulated mass. The cut surface is relatively uniform, with brownish areas corresponding to foci of haemosiderin deposition.

**Microscopic:** this example of schwannoma/neurilemmoma demonstrates the fascicles of spindle cells with nuclear palisading (Verocay bodies) which characterize Antoni A fields of Schwannoma (upper right corner). Antoni B areas, in contrast, have a loose and microcystic appearance in which spindle and oval cells are arranged haphazardly within loose matrix material (upper left corner). Hyalinised vessels and degenerative ‘ancient’ changes are also common features but not seen in this example.
Another example of nuclear palisading – Verocay bodies in schwannoma.

**Microscopy:** 2 types of fibres:-

1. fibrillary, intensely polar, elongated appearing tissue type called **tissue type A**. These cellular regions referred to as **Antoni A regions**.

2. loose microcystic tissue adjacent to the Antoni A regions known as **Antoni B regions**. Recognition of these patterns has proved useful in the histologic identification of schwannomas. **Antoni A and Antoni B regions** have been recognized as highly suggestive for the peripheral nerve sheath tumour schwannoma.

**Micrograph of Antoni A tissue** within a schwannoma. Wavy, tightly organized nuclear palisades known as Verocay bodies occupy the center of a highly cellular field.
In the example below, Antoni fields predominate in this schwannoma, with loose microcystic Antoni B on the bottom right.

The basement membrane found in Antoni A regions is rich in laminin, a high-molecular-weight glycoprotein, and is produced by Schwann cells at all stages of development. There is intense laminin positivity in schwannomas and neurofibromas and less intense positivity in leiomyomas and leiomyosarcomas, whereas fibrous histiocytes and fibrosarcomas generally are negative.

The immunohistochemical demonstration of attenuated *intercellular laminin* is a valuable aid in differentiating between tumours derived from Schwann cells and those derived from fibroblasts. Another component of basement membrane, collagen type IV, provides analogous antigen that is often targeted with diagnostic immunohistochemistry in clinical pathology laboratories. The adhesive properties of laminin are thought to explain the tight organization within Antoni A tissue.

Cells cultured with laminin express **S-100 protein** providing further support for their Schwann cell derivation. S-100 is a highly acidic protein found in many neural crest tumours and may play a role in the ionic regulation of nervous tissue. Although not specific, **S-100 protein is nonetheless a reliable marker for the diagnosis of schwannomas and is especially prevalent in the Antoni A areas**. In contrast, neurofibromas only show patchy positivity for S-100, because Schwann cells represent only a subset of the tumour constituency. MPNSTs contain only limited amounts of S-100 protein in roughly half of the cases. Its expression often corresponds with the degree of differentiation within these high-grade tumours.

**In the images below**, there is strong diffuse nuclear and cytoplasmic S-100 positivity. Collagen IV and laminin highlight prominent pericellular external lamina/basement membrane material, a constant feature of well differentiated schwann cells. EMA is restricted to peripheral perineurial cells related to the capsule.
Antoni B Regions

In contrast to the tightly organized Antoni A regions, the Antoni B regions tend to be relatively less cellular and contain more loosely arranged cells. Islands of type A and type B tissues usually appear fairly well demarcated from one another. The volume of Antoni B regions in any given tumour is variable and can occasionally be scant or completely lacking. Cells within the Antoni B regions are often thin and wispy, separated from one another by microcystic spaces filled with basophilic mucin. Microcysts may coalesce into radiologically detectable macrocysts. Cranial nerve VIII schwannomas have an abundance of Antoni B tissue, which may account for the frequently observed macrocystic regions. In addition, Antoni B tissue contains many lipid-laden histiocytes, lymphocytes, and small vessels with hyalinized walls.

The highly cellular Antoni A region on the right of the field is contrasted with the loosely organized hypocellular Antoni B region on left of the field.

Neoplastic Schwann cells in vitro show increased angiogenic properties similar to other tumour cells. The vascularization of these Antoni B areas is varied, sometimes aberrant or bizarre, but often contains degenerative features. Acute and chronic thrombosis, haemorrhage, and hyaline thickening of these ectatic vascular walls can be seen. Areas of frank necrosis further contribute to observed cystic regions.

Within type B tissue, areas of so-called “ancient change” may also be seen. Twisted cytoplasm and enlarged hyperchromatic and markedly atypical nuclei may be present without increased cellular attenuation or mitotic activity to denote anaplastic change. Prominent fibrous stroma is rarely punctuated by attenuated bands of hyalinized cartilage, particularly in mediastinal tumours. Cysts as
described above, focal calcification, and mucinous and xanthomous change involving the tumour cells are also common and thought to represent a degenerative phenomenon. Xanthomatous changes can produce areas that are yellow to the naked eye and that demonstrate aggregated foamy macrophages. Lymphocytic infiltrates are also relatively common.

Ancient change is characterised by scattered large hyperchromatic nuclei, a finding of no clinical significance – see micrograph above.

Separating the regions in many tumours is a **transitional zone with both Antoni A and B features**. This zone also contains detached segments of basal lamina debris, a diminished presence of S-100 protein, and strands of fibrin suggesting a degenerated Antoni A region. In addition, within Antoni B regions, some investigators have observed granules resembling myelin sheaths within presumably phagocytic vacuoles. Given these features, some researchers now contend that the Antoni B areas may embody degenerated Antoni A regions, with the transitional zone representing a stage in the deterioration process. The hyalinized blood vessels commonly encountered within Antoni B tissue may lead to ischemia, are prone to haemorrhage, and may further contribute to degeneration.

**Macroscopic**: post mortem example of a large CP angle acoustic nerve schwannoma
**Imaging:** Vestibular schwannoma. Enhanced T1-weighted MR image demonstrating a large predominantly cystic schwannoma arising from cranial nerve VIII within the internal auditory canal. The tumour fills the cerebellopontine angle, compresses the pons, and displaces the fourth ventricle. Debris settles within the dependent portion of the tumour.

**Imaging and Antoni Tissue Types**

Although imaging alone cannot consistently differentiate benign from malignant nerve sheath tumours or schwannoma from neurofibroma, the Antoni tissue types A and B patterns may have an impact on the neuroimaging features.

A heterogeneous MR imaging appearance of larger tumours was seen more commonly in lesions with a higher ratio of type B to type A tissue. This heterogeneous appearance also seemed related to other pathologic changes, mainly haemosiderin deposits and cystic formation seen within type B tissue. Increasing tumour size probably depends less on proliferation rate than on dystrophic changes, such as haemosiderin deposition and cyst formation and/or on the presence of type B tissue. Moreover, larger lesions may be inclined to degenerate as blood supply is compromised leading to degeneration, development of Antoni B tissue, and eventual cystic change on imaging.

Similarly, on CT, attenuated portions of schwannomas may correlate with Antoni A tissue, whereas hypotattenuated regions tend to correlate with Antoni B tissue. A so-called target sign has also been described in some nerve sheath tumours and consists of a central core of hypointensity surrounded by hyperintensity on T2-weighted and enhanced T1-weighted images. The central region contains fibrocollagenous tissue, and the peripheral region consists of myxomatous tissue; however, histologic correlation often fails to reveal a consistent association with tumour type or Antoni A or Antoni B regions.

Antoni A and B tissue types represent distinct histologic architectural patterns that aid in the pathologic diagnosis of schwannomas and may influence their imaging characteristics. Type A tissue is highly cellular and demonstrates nuclear palisading and associated Verocay bodies, which may reflect their prominent extracellular matrix and secretion of laminin. Type B tissue is loosely organized with myxomatous and cystic changes and may represent degenerated Antoni B.

**Molecular biology schwannomas**

Schwannomas, both sporadic and those associated with neurofibromatosis type 2 (NF2), most commonly show deletion of the *NF2* locus known as 22q12.2 (rare translocations have also been
The NF2 gene encodes merlin (i.e. schwannomin), a tumour suppressor protein of which the expression is typically lost in most schwannomas.

Although the mechanism by which merlin influences the cell cycle is not fully understood, recent studies describe merlin's interaction with and inhibition of several proteins involved in the cell cycle and mitogenic signal intensity transduction.

These proteins include the following:

**MLK3 (mixed lineage kinase 3)**, which stabilizes the B-Raf/Raf-1 complex within the mitogen-activated protein kinase pathway and is required for schwannoma tumour cell proliferation,

**HEI10**, which controls the accumulation of cyclin B, a protein critical to cell cycle control and

**GTPase PIKE-L (phosphatidylinositol 3-kinase [PI3Kinase] enhancer)**, which promotes cell survival by activating PI3Kinase.

**Schwannomatosis (NFIII)**

is one form of neurofibromatosis (NF) that has only recently been recognized and is sometimes called neurofibromatosis type III. Originally described in Japanese patients it consists of multiple cutaneous schwannomas, central nervous system tumours, and other neurological complications, excluding hallmark signs of NF. It is not associated with the genetic abnormalities associated with NF1 or NF2 and the majority of cases are sporadic. It is a rare disorder, affecting around 1 in 40,000 individuals.

**Criteria for the diagnosis** of the disorder are:- **Definite category;**

- Age >30 years and ≥2 nonintradermal schwannomas, at least one with histologic confirmation and no evidence of vestibular tumour on MRI scan and no known NF mutation, or One nonvestibular schwannoma plus a first-degree relative with schwannomatosis

**Clinical features of schwannomatosis:**

Many of the symptoms of schwannomatosis overlap with NF2.

- Schwannomas occur instead of the neurofibromas that are hallmarks of neurofibromatosis Type 1.
- Multiple schwannomas manifest throughout the body or in isolated regions.
- The schwannomas develop on cranial, spinal and peripheral nerves
- Chronic pain, and sometimes numbness, tingling and weakness.
- About 1/3 of patients have segmental schwannomatosis, i.e. the schwannomas are limited to a single part of the body, such as an arm, a leg or the spine
- There are several cases where people with schwannomatosis have developed a vestibular schwannoma (acoustic neuroma). This nerve is involved in hearing and patients with vestibular schwannomas experience hearing loss. However, bilateral vestibular schwannomas (vestibular schwannomas on both sides of the brain) do not occur in schwannomatosis. Juvenile vestibular tumours do not occur either.
- Patients with schwannomatosis do not have learning disabilities related to the disease.
- Symptoms are sometimes brought on by hormonal changes such as puberty and pregnancy.
**Macroscopic:** The example below shows two schwannomata involving a peripheral nerve in schwannomatosis.

A representative section of a schwannomatosis specimen illustrated below demonstrating an intraneural schwannoma.

**Treatment:** Schwannomatosis patients represent 2.4% to 5% of patients undergoing surgical resection of their schwannomas
Cellular schwannomas characteristically form large deep seated lesions, particularly in the retroperitoneum and mediastinum. They typically arise from large nerves, are encapsulated, minimally invasive but may be associated with destructive local effects e.g. eroding surrounding structures such as bone as they increase in size.

Microscopic:

The above example of cellular schwannoma highlights a crowded spindle cell proliferation, resembling hypercellular Antoni A tissue of conventional schwannoma/neurilemmoma. The crowded fascicles of cells of cellular schwannoma however demonstrate a degree of nuclear pleomorphism, hyperchromaticity and mitotic activity. Cellular schwannoma must be distinguished from malignant peripheral nerve sheath tumours (MPNST). Other important features include the finding of encapsulation, hyalinised vessels, capsular lymphocytic aggregates and foamy histiocytes.
Cellular schwannoma must be distinguished from a number of other spindle cell neoplasms such as leiomyosarcoma, GIST and MPNST.

Unlike most MPNST of spindle cell morphology, cellular schwannoma demonstrates strong diffuse S100 protein positivity – see below.
PLEXIFORM SCHWANNOMA VARIANT – WHO grade I

The above example illustrates the plexiform pattern of schwannoma – the neoplastic schwann cells involve and expand pre-existing nerve fascicles. This pattern of multinodular involvement results in the characteristic plexiform pattern.

**Treatment:** surgical removal should result in cure.

**MELANOTIC SCHWANNOMA – 9560/1 (psammomatous melanotic schwannomas).**

In addition to basic features of schwannoma, this tumour often has heavy pigmentation due to the presence of melanin-producing cells with ultrastructure features of Schwann cells.

**Sites:** spinal nerves (90%), arises commonly in the paraspinal sympathetic chain.

**Incidence:** rare tumour.

**Age:** tends to affect young adults.

**Gender:** slight female preponderance – 1.4 : 1

**Clinical:** usually a long history of backache.

**Associated conditions:** 55% occur in association with the Carney complex (myomas, spotty pigmentation and endocrine over-activity.

**Pathogenesis:** the melanotic variant has a significant incidence of malignant behaviour with metastases reported in 25% of cases.

**Differential diagnosis:** melanoma. Differs from melanoma in its tendency to recur at the site of excision and slow rate of growth.
**Macroscopic:** the tumour appears jet black – see example below.

**Microscopic:** There are epithelioid and spindle cells with abundant melanin pigment (brown) – see below.
Another example shows the morphology almost completely obscured by abundant melanin pigment.

A case showing spindle cell morphology with less abundant melanin pigment.

Images which follow, courtesy of Welling LC, Guirado VMP, Tessari M, Felix AR, Zanellato C, Fiqueiredo, Taricco MA, Teixeira MJ. Arq Neuro-Psiquiatr 2012; 70(2) show -

(A) MRI images showed intradural, extramedular lesions isointense/hyperintense in T1.
(B) The histological examination revealed fusiform and epithelioid cells, with highly pigmented cytoplasm.
(C) Immunohistochemical studies revealed intense cytoplasm and nuclear expression of S100 protein
(D) HMB-45 and Melan-A (D).
**Treatment:** total resection should be performed and long-term follow-up is needed as it may recur or metastasize after more than 5 years, even in the absence of overt malignant histological features.

**NEUROFIBROMA – 9540/0 – WHO grade I**

**Definition:** A neurofibroma is a benign nerve sheath tumor in the peripheral nervous system.

**Site:** In 90% of cases they are localized, while 10% are found in persons with neurofibromatosis type I (NF1), an autosomal dominant genetically inherited disease.

**Incidence:** neurofibromas constitute 5% of all benign soft tissue tumors.

**Origin:** Neurofibromas arise from nonmyelinating-type Schwann cells that exhibit biallelic inactivation of the NF1 gene that codes for the protein neurofibromin. This protein is responsible for regulating the RAS-mediated cell growth signaling pathway. In contrast to schwannomas, neurofibromas incorporate many additional types of cells and structural elements in addition to Schwann cells.

**Anatomy:** Diagram of a neurofibroma. The endoneurium (dark yellow) increases in volume. Schwann cell cylinders (light brown) separate from one another and become dolichoectatic. The mature tumour consists of a complex of Schwann cells, axons, and fibrous material within a myxomatous matrix surrounded by a thickened perineurium (tan and dark brown).
**Clinical:** they can result in a range of symptoms from physical disfiguration and pain to cognitive disability. They can involve superficial or deep nerves.

**Macroscopic:** Specific neurofibroma subtypes relate to architectural growth pattern and include localized, diffuse and plexiform forms. The neoplasm and the nerve cannot be separated. The example below is a localised neurofibroma excision specimen demonstrating typical nodular type growth, encapsulation and uniform appearance to the cut surface.

Images below – shows the dumb-bell shape of a spinal neurofibroma. Drawing courtesy of Dr. Aleta Ann Frazier.

**Microscopic:** Neurofibromas appear to contain all the cellular elements of a peripheral nerve, including Schwann cells, fibroblasts, perineurial cells, and axons. The tumour cells grow diffusely within and along nerves, causing the nerves to expand radially while entrapping native neural elements within the substance of the tumour. This intraneural growth pattern, with its entrapped axons, provides a key feature to histologically distinguish neurofibroma from schwannoma.
This example above of neurofibroma is formed by cells having slender wavy nuclei which are separated by stroma containing bundles of collagen and pools of lightly staining myxoid material. The proportions of these three tumour constituents (spindle cells, collagen and myxoid stroma) may vary within the same tumour.

**Immunohistochemistry:**  **S-100** positivity in Schwann cell component, EMA and Claudin-1 highlight perineurial component and NF(neurofilament) stain shows small axonal processes.
Imaging: Solitary neurofibroma in a 34-year-old woman.

A, Enhanced fat suppressed T1-weighted MR axial image at the L4–5 level demonstrates an enhancing tumour arising from the left L4 root. The neural foramen is expanded.

B, Photograph of cut sections of the gross specimen in the same patient shows a solid heterogeneous-appearing tumour, which has grown within and expanded multiple fascicles of the nerve.

Treatment: complete resection requires sacrifice of the nerve, so deep-seated lesions are often managed conservatively with observation.

PLEXIFORM NEUROFIBROMA – 9550/0 – WHO grade I

Diagram by Dr Aleta Ann Frazier, shows a plexiform neurofibroma with all nerves involved.
When a neurofibroma involves multiple branches of a nerve plexus or multiple fascicles within a large nerve, it adopts and amplifies the normal anatomic tortuosity to produce a “plexiform” growth pattern that has been likened to a bag of worms.

Site: Plexiform neurofibromas most commonly occur in the orbit, neck, back, and inguinal areas, most occurring in patients with neurofibromatosis type 1 (NF1).

Imaging: Plexiform neurofibroma in a 21-year-old man with no other signs of NF1. Sagittal enhanced T1-weighted MR image demonstrates an enhancing serpentine mass in the pontine soft tissues of the neck.

Molecular Biology:

Neurofibromas also demonstrate loss of a tumour suppressor gene NF1, located on chromosome 17q12. This gene encodes the tumour suppressor protein neurofibromin. Cells deficient in this protein demonstrate altered actin cytoskeletons, increased cell motility, increased cell proliferation, and elevated activity within the RAS signaling pathway. Neurofibromin has been identified as a GTPase activating protein for the GTPase oncoprotein K-RAS. By facilitating GTPase activity of K-RAS, neurofibromin effectively inhibits K-RAS, preventing K-RAS from activating the tuberous sclerosis complex/mammalian target of rapamycin pathway. In this manner, neurofibromin inhibits proliferation.

Prognosis: Although benign lesions with a generally favorable prognosis, the ultimate treatment outcome for both schwannomas and plexiform neurofibromas depends largely on size, location, and therapy.

NEUROFIBROMATOSIS (von Recklinghausen’s disease)

In this disorder neural and fibrous components are associated. 8 variations have been described but NF1 and NF2 account for 99% of the cases.

NF1 - musculo-skeletal abnormalities predominate. Variant forms of NF1 include segmental, gastrointestinal, spinal and familial café au lait spots.
To make a **diagnosis of NF1**, two or more of 7 criteria have to be present viz.

- Six or more café au lait spots
- Two or more neurofibromas (any type), or one plexiform neurofibroma (pathognomonic)
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- Osseous lesions e.g. sphenoid dysplasia and pseudoarthrosis
- First-degree relative with NF1

Classic triad is cutaneous lesions, skeletal deformity (especially kyphoscoliosis) and mental deficiency. The hallmark for diagnosis is the neurofibroma.

**Incidence of NF1** - 1 in 3000 births

**Sites:** can occur in any location of the body including soft tissues superficial and deep, and viscera. In NF1 the sciatic nerve and brachial plexus are more frequently involved.

**Age:** neurofibromas usually occur initially in childhood or teenagers, subsequent to the detection of café-au-lait spots.

**Gender:** slight predominance in males.

**Genetics:** When inherited it is as an autosomal dominant trait but new mutations cause 50% of NF1 cases. The genetic abnormality is on chromosome 17, the site of a tumour suppressor gene. This focus encodes the production of the 2,800 amino acid protein neurofibromin that is thought to have some role in the control in cell growth regulation and so its loss results in production of tumours.

**Risk factors:** advanced paternal age > 35 years present in 80% of cases.

**Pathogenesis of NF1:** malignant transformation to MPNST varies from 2% to 29%. Numerous additional neoplasms may be associated with NF1 – optic glioma, astrocytoma, glioblastoma multiforme, rhabdomyosarcoma, triton tumour, phaeochromocytoma, carcinoid tumour, nephroblastoma, gastrointestinal stromal tumour and juvenile chronic myeloid leukaemia

**Treatment:** as there are usually multiple lesions and/or deep lesions, surgery is kept for only those that are causing symptoms.

**Medical regimes** in the early 2000s with cis-retinoic agent (maturational agent), interferon alpha (anti-angiogenic agent), tibifarnib (protein inhibitor), perfinidone (anti-fibrotic agent) and thalidomide (antiangiogenic agent) have had beneficial effects in terms of stabilizing lesion growth and even reversal.

**Intracranial manifestations of NF1** – images that follow are courtesy of O’Brien WT. JAOCR April 15 2015.

Intracranial CNS manifestations include characteristic NF1 “spots” and low-grade neoplasms. The NF1 “spots” – see arrows - are regions of signal abnormality involving the basal ganglia, thalami, dentate nuclei, cerebellar peduncles, optic radiations, and brainstem in children and adolescents; they are thought to represent regions of myelin vacuolization. They are hyperintense on T2 sequences and typically iso- to mildly hyperintense on T1 images. There should be no mass effect or
enhancement, as enhancement or significant mass effect suggests development of a low-grade glioma. The lesions may wax and wane for the first decade of life or so and then regress. They are uncommon after the second decade of life.

**Sphenoid wing dysplasia.** Axial CT image in bone window reveals anterior displacement and thinning of the sphenoid bone on the right with enlargement of the middle cranial fossa in the anteroposterior dimension. A soft tissue mass extending through and expanding the right optic canal, consistent with an optic pathway glioma, is partially seen.

**Bilateral optic nerve gliomas:**
Buphthalmos. Axial CT image reveals enlargement of the right globe in a young child with NF1, consistent with buphthalmos.

Plexiform neurofibroma. Coronal fluid-sensitive T2 * images with fat suppression demonstrate a large enhancing T2 hyperintense mass with intermediate to hypointense linear striations involving the pre- and postseptal compartments of the left orbit, as well as involvement of the suprazygomatic masticator space on the left. There is mass effect on the left with proptosis.

Spinal (plexiform) neurofibromas. Axial (A) and coronal (B) T1 postcontrast images with fat suppression reveal multiple, large, lobulated, enhancing paraspinal, extradural, and intradural extramedullary masses. Cord compression is seen at the cervicomedullary junction. The coronal image (B) shows focal scoliosis within the upper thoracic spine associated with numerous paraspinal masses, as well as foraminal extension and expansion within the upper cervical spine. There is partial collapse of the left upper lobe.
NEUROFIBROMATOSIS NF2 – CNS manifestations e.g. bilateral acoustic neuromas, gliomas and meningiomas

ATYPICAL NEUROFIBROMA variant 9540/0 – WHO grade 1 in NF1

Some neurofibromas may demonstrate cytological atypia (which may be degenerative ‘ancient type’ atypia) and/or demonstrate increased cellularity, prompting consideration of a malignant peripheral nerve sheath neoplasm, particularly when occurring in the setting of NF1 and may be regarded as a pre-malignant lesion.

Benign peripheral nerve sheath tumors (BPNSTs) are a characteristic feature of neurofibromatosis type I (NF1) patients. NF1 individuals have an 8-13% lifetime risk of developing a malignant PNST (MPNST).

Microscopic: Atypical neurofibromas are symptomatic, hypercellular PNSTs, composed of cells with hyperchromatic nuclei in the absence of intermediate-, and high-grade by karyotyping and microarray-based comparative genome hybridization (aCGH).

Atypical neurofibroma - above - characterized by scattered individual cells demonstrating marked cytologic atypia in the absence of features diagnostic of malignancy (MPNST).

Molecular biology: One highly significant recurrent aberration was identified in the atypical neurofibromas, namely a deletion with a minimal overlapping region (MOR) in chromosome band 9p21.3, including CDKN2A and CDKN2B.

Copy number loss of the CDKN2A/B gene locus was one of the most common events in the group of MPNSTs, with deletions in low-, intermediate-, and high-grade MPNSTs. May see clear transition from a benign-atypical neurofibroma toward an intermediate-grade MPNST, confirmed by both histopathology and aCGH analysis. These data support the hypothesis that atypical neurofibromas are premalignant tumours, with the CDKN2A/B deletion as the first step in the progression toward MPNST.
IMAGING of Swannoma, neurofibroma, neurofibromatosis and MPNST (WHO gr 2 – 4).

Plain radiography: may show a non-specific soft tissue mass which, in neurofibromas, may show calcification if there are areas of chondroid, osteoid tissue within the tumour tissue. Latter more common in MPNST and large tumours.

Ultrasound is useful to demonstrate plexiform and localized neurofibromas in limbs.

MRI – can show the fusiform shape of the tumour with entering and exiting nerve. There may be associated muscle atrophy.

Distinction of MPNST versus BPNST - imaging features favouring malignancy include size greater than 5 cm, prominent vascularity, marked heterogeneity, central necrosis, rapid growth, increased gallium uptake, and evidence of infiltrative margins in a non-plexiform lesion.

Imaging of Malignant peripheral nerve sheath tumour. MRI Coronal T2 image demonstrates a large dumbbell-shaped mass extending through and expanding a neural foramen within the lumbar spine on the left. The superior portion of the intraspinal component is ill-defined and increased in size from comparison examination. Multiple NFs are seen at adjacent levels.
PERINEURIOMAS – 9571/0 – WHO grade I

**Definition:** is a rare tumor of the perineurial cells, the type of cells that are present around a peripheral nerve sheath. These tumors are generally benign in nature, but may be occasionally malignant. Two distinct types are recognized, those that involve nerves i.e. intraneural and those that occur in soft tissue.

**Incidence:** Perineuriomas are exceedingly rare, representing less than 1% of nerve sheath tumours.

**Site:** They most commonly affect peripheral motor nerves, but sensory and cranial nerve involvement has also been reported.

Soft tissue perineurioma occur in a wide age range, may involve the limbs or trunk and occur more commonly in subcutaneous than deep soft tissue sites.

**Macroscopic:** The intraneural perineurioma results in enlargement and expansion of the involved nerve, as illustrated in the surgical resection specimen below.

![99B5821D](image)

**Microscopic:** These tumours are formed by neoplastic perineurial cells arranged into “pseudo-onion bulbs” around axons within the perineurium and endoneurium of nerve fascicles. Thus, axon entrapment distinguishes both perineuriomas and neurofibromas from schwannoma. In contrast, “extraneural” soft tissue perineuriomas do not display entrapped axons. The latter are not encountered in the CNS.

The cross section of nerve below demonstrates multilayered concentric cuffs of perineural cells which surround and envelop axonal processes. These collections, referred to as **pseudo-onion bulbs**, are characterized by EMA positivity.
Macroscopic of a soft tissue perineurioma: these lesions are well circumscribed, unencapsulated and lack an associated nerve.
**The soft tissue perineurioma** demonstrates delicate long spindle cells which lie in a fibrous stroma and form very long and slender cytoplasmic processes. EMA positivity is useful in confirming the perineural nature of the spindle cell population.

Soft tissue perineuriomas may demonstrate a variety of microscopic appearances, including lamellar (shown above) and reticular (below) architectural patterns. The perineurial cells elaborate extremely long delicate cytoplasmic processes. Sclerosing perineurioma is another distinctive variant often involving the hands of young adults.
MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR (MPNST) – 9540/3

**Definition:** the term MPNST is used for malignant tumours arising from, derived from, or replicating intrinsic peripheral nerve cells i.e. the Schwann cell and the perineurial cell. Tumours that arise in the epineurium and blood vessels of the nerve are excluded. It does include malignant forms of neurofibromas and schwannomas. 60% derived from neurofibromas. Others arise de novo from nerve.

The perineurial cell MPNSTs are very uncommon (4% of MPNSTs) so one is mainly concerned with those of Schwann cell differentiation.

**Sites:** MPNST appears in the same areas as plexiform neurofibroma, close to a plexus of nerve trunk – brachial or sacral - but the common sites of origin that impact the CNS are cranial nerve V and the spinal roots; cranial nerve VIII is only rarely involved.

**Incidence:** They are estimated to account for 5-10% of all soft-tissue sarcomas

**Age:** typically present in adults.

**Gender:** No predilection

**Clinical presentation:** varies depending upon location.

**Associations:** neurofibromatosis type I – in 25 – 70% of cases. Also previous irradiation.

**Pathophysiology:** The MPNST may develop either de novo or from transformation of a plexiform neurofibroma or schwannoma in a patient with NF1. Very rarely, MPNST may arise from a benign schwannoma.

**Macroscopic:** As illustrated below, MPNST are often fusiform or globoid, are pseudoencapsulated and demonstrate a variegated cut surface—cream to tan, firm to soft, often haemorrhagic and necrotic.
**Microscopic:** MPNST demonstrates diverse microscopic appearances. They often appear as an invasive hypercellular spindle cell lesion with only subtle features to distinguish it from other sarcomas. The example below illustrates a largely fascicular spindle cell proliferation, which is characterized by nuclear pleomorphism and brisk mitotic activity. The malignant cells surround a vessel to produce an angiocentric pattern, a feature of MPNST.

Alternating fields of hypercellular and hypocellular growth as illustrated below, are a clue to the diagnosis.
Concentration of tumour cells around blood vessels, as illustrated above, is another characteristic of MPNST.

90% are high grade with mainly spindle cells, hypercellularity, hyperchromasia, fascicular growth, high mitotic activity, sharply outlined patches of necrosis.

10% that are low grade have spindle cells, mild to moderate cellularity, nuclei at least three times larger than normal Schwann cell nuclei and low mitotic activity but generally no necrosis.

A small percentage are epithelioid and 15% show divergent differentiation in the form of heterologous mesenchymal or glandular tissue. A few tumours will have exclusively perineurial cell differentiation.

**Immunohistochemistry:**  S-100 protein is the one most frequently employed because of its great sensitivity for cells of this tumour – 50-70% are positive for this marker. Leu-7 is the second most often used marker but when it is positive it cannot distinguish between tumours with Schwann cell and perineurial cell differentiation.

**Molecular biology:** complex karyotype with numerous structural and numerical changes. Alterations of cell cycle regulators p53,p16 and p27.

**Radiographic features**

Imaging criteria are generally considered unreliable in differentiating from a more benign neurofibroma or schwannoma.
However in favour of a MPNST include:

- the larger the lesion, the more likely for it to be malignant
- irregular borders (although most MPNSTs can have well defined margins)
- rapid growth on interval imaging

**CT image below, courtesy of Assoc. Professor Frank Gaillard Radiopaedia.org. rID 5219 shows the tumour arising from the sacral plexus, destroying adjacent sacrum and right iliac bone.**

Another local patient, male aged 34 yrs, who at the time of presentation had metastases in the lungs. The arrow indicates the lateral perimeter of the tumour which has destroyed adjacent sacrum and iliac bone.

**Chest radiograph shows multiple metastases – arrows on those in the right lung and others are present in the left lung.**
MRI

- **T1**: usually isointense to muscle; heterogeneous signal on T1 (if present) may be useful in differentiating from a neurofibroma
- **T2**: can have low signal due to high collagen content

**Scintigraphy**

Gallium scintigraphy may show higher uptake than that of a neurofibroma

**Treatment and prognosis**: It is an aggressive tumour that carries an extremely poor prognosis.

**EPITHELIOID VARIANT OF MPNST**

is characterized by malignant cells with rounded or polygonal nuclei, prominent nucleoli and relatively abundant cytoplasm and can mimic the microscopic appearances of carcinoma and epithelioid melanoma..

**MPNST variant** (MPNST with divergent mesenchymal differentiation).
This malignant peripheral nerve sheath tumour is an example of a malignant triton tumour. Scattered rhabdomyoblasts, with large pleomorphic nuclei and abundant fibrillary eosinophilic cytoplasm, which represent foci of divergent skeletal muscle differentiation, are seen within the background of malignant peripheral nerve sheath tumour.

MPNST variant with perineural differentiation  (Malignant perineurioma)- 9540/3

The great majority of malignant peripheral nerve sheath tumours (MPNST) exhibit Schwannian differentiation. In recent years, a subset of perineurial MPNST (malignant perineurioma) has been identified based on their histologic, immunohistochemical and ultrastructural features. **Immunopositivity for epithelial membrane antigen (EMA), glut-1 and claudin-1, is characteristic.** Such tumours must be distinguished from benign perineurioma and a variety of atypical or malignant soft tissue tumours featuring EMA positivity

**Prognosis of MPNSTs:** Unlike schwannoma and neurofibroma, which are benign tumours with favorable prognosis, that of MPNST is generally poor. Metastases may develop in the lung, liver, and brain, and, therefore, primary treatment is usually aimed at local control through wide excision when possible. Chemotherapy and radiation therapy are also considerations.

Local recurrence is 40 – 65% and metastasis occurs in up to 80%.

Overall 5-year survival is 40%. 
NEUROMA – this is not a true soft tissue neoplasm but represents lesions of nerve caused by reactive hyperplasia.

Types: traumatic, Morton, mucosal, Pacinian and palisaded encapsulated neuromas.

Traumatic neuroma typically arises in the setting of injury to a peripheral nerve, as the name implies (eg, brachial plexus injury associated with obstetric delivery); the resulting mass develops from the nerve’s regeneration and a fruitless attempt to re-establish its connections. Histologically, the mass appears as a jumble of benign-appearing nerve minifascicles interwoven with reactive fibrous tissue. If the nerve ends of an injured nerve are approximated surgically, it reduces the chance of this condition developing.

The above example is an amputation specimen of a traumatic neuroma, the non-neoplastic mass expanding a nerve trunk.

Morton neuroma represents perineural fibrosis of the plantar digital nerve likely related to chronic injury and is not a neoplasm. Surgical resection of the neuroma and involved nerve segment is the most successful treatment.

Mucosal neuroma affect the mucosal surfaces of the mouth, lips, eyelids and intestines. See in patients with multiple endocrine neoplasia. The neuromas are frequently an early manifestation of disease in the first several decades of life.

Pacinian neuroma arise from hyperplasia or hypertrophy of the Pacinian corpuscle which are mechanoreceptors and most numerous in the deep skin layers of the hands and feet. Also occur in viscera walls, mesentery and vessel wall adventitia. Present as small superficial masses affecting the hands and feet, especially the index and long fingers near the periosteum along the lateral portion of the proximal and middle phalanges or beneath the flexor tendons at the level of the base of the proximal phalanges. Associated with a history of trauma. Surgical excision with preservation of the nerve is curative.

Palisaded encapsulated neuroma develop as a small asymptomatic subcutaneous nodule affecting the face. Not associated with trauma and are encapsulated. Surgical excision is curative.
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