

Peripheral nerve tumours

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INTRODUCTION

- Peripheral nerve tumours are growths in or near the strands of tissue (nerves)
- They are a heterogeneous group of mostly benign tumours that are rare in the general population.
- Although benign, they can lead to pain, nerve damage and loss of function in the affected area.
- Certain types, including neurofibromas and schwannomas, may occur sporadically or in association with neurofibromatosis

CLINICAL PRESENTATION

- Symptoms and signs of peripheral nerve tumours are caused by direct nerve invasion, involvement of surrounding tissues, or mass effect.
- There are no specific clinical presentations unique or even especially suggestive of a particular nerve tumour, with the exception of neurofibromatosis type 1 and type 2.
- As the tumour grows, it may be more likely to cause signs and symptoms, although tumour size doesn't always determine effects.
- Patients present for evaluation of peripheral nerve tumours because of a soft tissue mass, pain, or focal neurologic findings, approximately in that order of frequency.

CLINICAL PRESENTATION

- The duration and progression of symptoms or signs are important, as most benign tumours have a longer duration and a slow rate of progression, while malignant tumours tend to progress rapidly in size, amount of pain, and neurologic deficit.
- Any mass changing its clinical character should be taken seriously, as that is one of the few clinical clues to its potentially malignant nature. In particular, rapidly expanding soft tissue masses in patients with NF are very suspicious for the presence of a malignant peripheral nerve sheath tumour and should be evaluated promptly.
- A careful family history is important in the assessment of an underlying neurogenetic disorder, such as Neurofibromatosis.

AETIOLOGY

- It's not clear why most peripheral nerve tumours develop.
- Some are linked to known inherited syndromes, such as neurofibromatosis (types 1 and 2) and schwannomatosis.
- Others may be caused by a malfunctioning gene or triggered by injury or surgery.

RISC FACTORS

- **Neurofibromatosis (types 1 and 2) and schwannomatosis.** In these disorders, tumours develop on or near the nerves throughout the body. These tumours, which are frequently multiple, can lead to a variety of symptoms and signs depending on their location.
- **A history of radiation treatment.** If you were exposed to radiation, you are at increased risk of peripheral nerve tumours.

COMPLICATIONS

- Both noncancerous and cancerous peripheral nerve tumours can compress nerves, leading to complications, some of which may be permanent:
 - Numbness and weakness in the affected area
 - Loss of function in the affected area
 - Difficulties with balance
 - Pain

➤ BENIGN NON-NEOPLASTIC NERVE TUMOURS

- Neuroma
- Ganglion cyst
- Intraneural heterotopic ossification
- Sacroid Granuloma
- Inflammatory pseudotumour of nerve
- Leprosy
- Hypertrophic neuropathy
- Miscellaneous

NEUROMA

- Benign nonneoplastic overgrowth of nerve fibers and Schwann cells
- Usually post-traumatic; proximal nerve regenerates into a tangled mass of nerve fibers if it does not meet the distal end
- Painful.

NEUROMA – MORTON NEUROMA

- Morton's neuroma is one of the most common causes of metatarsalgia.
- Nonoperative treatment is successful in a limited percentage of cases, but it can be adequate in those who want to delay or avoid surgery.
- Dorsal or plantar approaches were described for surgical treatment, both with strengths and weaknesses.
- Failures are related to wrong diagnosis, wrong interspace, failure to divide the transverse metatarsal ligament, too distal resection of common plantar digital nerve, an association of tarsal tunnel syndrome and incomplete removal.

INTRANEURAL GANGLION CYSTS

- They are benign mucinous lesions that are formed within peripheral nerves.
- Typically they lead to symptoms and signs of peripheral neuropathy.
- Their pathogenesis has been controversial.
- Different treatments have been recommended.
- Outcomes have been disappointing and the recurrence rate high and underreported.

INTRANEURAL GANGLION CYSTS - Intraneural ganglion cysts: a systematic review and reinterpretation of the world's literature. J Neurosurg 125:615–630, 2016

- Intraneural cysts are not rare. They are becoming diagnosed increasingly and reported more frequently now that imaging of nerves is being performed at a higher rate.
- Joint connections are becoming increasingly identified, especially in cases in which MRI is used. Since the end of 2003, of the total amount of reported joint connections, a greater percentage of joint connections have been described, with 61% being reported since this date.
- Intraneural recurrences are becoming increasingly recognized. We believe that this is due to the increasing awareness of joint connections, the increasing use of MRI and the better follow-up of these patients. We wish to emphasize that joint connections have been consistently identified when initial or postoperative images from these cases have been scrutinized. We predict that the percentage of intraneural recurrences will decrease as treatment paradigms change and target the articular branch connection. They recommend treating the articular branch connection and/or the joint.
- Failure to disconnect the articular branch or treat the joint pathology has been found to be a statistically significant risk factor for cyst recurrence.

INTRANEURAL HETEROTOPIC OSSIFICATION

- It is a rare condition of the peripheral nerves which can mimic myositis ossificans in both histologically and radiologically.
- There is usually a history of injury.
- Surgical resection of the lesion, although eliminating pain, will in case of motor branches cause a motor deficit.

SARCOID GRANULOMAS

- Peripheral neuropathy is a rare, yet treatable manifestation of sarcoidosis, a multisystem disorder characterized by the presence of non-caseating granulomas that are seldom found in nerve biopsy specimens.
- Wide range of clinical manifestations.
- Frequent association of granulomatous inflammatory infiltrates with necrotizing vasculitis and with silent or symptomatic involvement of other organs.

INFLAMMATORY PSEUDOTUMOUR OF NERVE

- Inflammatory pseudotumour of nerve is not a neoplasm and has reactive features of inflammation, increased vascularity, and marked fibrosis.
- It presents as a progressive axonal mononeuropathy with weakness, sensory loss, and pain that may be episodic.
- The primary pathophysiology is unknown but the inflammation and response to treatment (steroids) suggests that there may be an immune component.

LEPROSY

- Leprosy is the most common treatable cause of neuropathy in the world.
- In all patients with leprosy, the nerve tissue is involved.
- The dermal nerves are infected in all skin lesions, including those due to indeterminate leprosy of childhood.
- It is well known that the sensory nerves are first to be affected in leprosy, but it also can lead to sensory, motor or autonomic deficit.
- If the preclinical damage is detected early in the course of disease, it can be prevented to a large extent.

HYPERTROPHIC NEUROPATHY

- It is a rare entity commonly associated with peripheral nerve, characterized by onion bulb formations.
- Severe, early childhood form of Charcot-Marie-Tooth disease.
- It is characterized by sensory loss with ataxia in the limbs furthest from the body and pes cavus with progression towards the limbs closest to the body.

➤ BENIGN NEOPLASMS OF NON-NEURAL SHEATH ORIGIN

- Desmoid tumour
- Neurothekeoma

DESMOID TUMOUR

- They are locally aggressive lesions of connective tissue origin that infiltrate surrounding tissues.
- They have a marked propensity for persistence or recurrence.
- Although most authorities regard these lesions as benign, it can be locally very aggressive.
- These lesions occur most frequently in the anterior abdominal wall of women who have borne children.
- Microscopically they contain abundant collagen with uniform elongated spindle cells.
- Radical surgical resection followed by radiation therapy seems to be the best protocol.

NEUROTHEKEOMA

- Neurothekeomas are rare, benign, superficial, soft tissue tumours of unknown histogenesis, although fibrohistiocytic derivation has been suggested.
- On histology, the cellular variant of neurothekeoma will appear as a bland, cellular, epithelioid proliferation that demonstrates strong immunoreactivity for vimentin, MITF-1, CD10, and NKI-C3.
- Neurothekeomas are classically described as benign, superficial cutaneous tumours with variable histologic patterns, including myxoid, cellular, or mixed-type based primarily on the amount of myxoid matrix present.
- Because of overlapping clinical presentation and histology, nerve sheath myxoma has, in a past case study series, been inadvertently included within the myxoid variant of neurothekeoma. However, neurothekeoma, as described by Barnhill and Mihm in 1990, appears to be a separate and distinct entity from true nerve sheath myxoma. While nerve sheath myxoma demonstrates immunoreactivity for S-100 protein, neurothekeoma fails to react with S-100 regardless of the histologic pattern (myxoid, mixed, or cellular).
- Rather than arising from peripheral nerve sheath, it has been postulated that neurothekeomas are of fibrohistiocytic derivation.
- They frequently occur in the head and neck and tend to affect females more often than males, usually in the second and early-third decades of life.

NEUROTHEKEOMA

- Clinically, neurothekeomas are usually asymptomatic and found in the skin and the superficial dermis. Mucosal involvement is rare.
- Patients typically present with a solitary mass measuring less than 2.0 cm, appearing dome-shaped, papular, or nodular with a pink-tan to reddish-brown.
- The lesions tend to grow slowly and are usually superficially located, with rare, deeper involvement of skeletal muscle or subcutaneous fat.
- Patients tend to be young females and typically present with an asymptomatic, slow-growing solitary dermal nodule of the head and neck, shoulder, or upper extremities measuring less than 2 cm.

NEUROTHEKEOMA

- Treatment consists of surgical excision.
- There is no consensus on excision margin, but clear microscopic margins and a few millimeters of grossly negative margins are thought to be sufficient.
- While the majority of these tumours are small (less than 1 cm) and have relatively bland histology, with scant to no cytologic atypia and minimal extension into surrounding fat or skeletal muscle, there have been reports of neurothekeomas displaying atypical features, increasing concern for aggressive potential.
- Reported atypical features include clinical size greater than 1 cm, cytologic atypia in the form of pleomorphism and increased mitotic activity, infiltration into skeletal muscle or subcutaneous fat, and vascular invasion. Regardless of the presence of atypical features, reported recurrence rates remain low following complete surgical excision.

➤ BENIGN NERVE SHEATH NEOPLASMS

- Neurofibroma
- Schwannoma
- Perineurioma
- Hybrid nerve sheath tumours
- Dermal nerve sheath myxoma
- Gangioneuroma
- Hemangioblastoma

NEUROFIBROMA

- Neurofibromas are the most prevalent benign peripheral nerve sheath tumours.
- Often appearing as a soft, skin-colored papule or small subcutaneous nodule, they arise from endoneurium and the connective tissues of peripheral nerve sheaths.
- Neurofibromas are comprised of Schwann cells, fibroblasts, perineural cells, and mast cells in a variably myxoid background.
- A mutation in the NF1 gene causes neurofibromas.
- There are three main types of neurofibromas: localized (most common), diffuse, and plexiform.
- Although the majority of neurofibromas occur sporadically and have an extremely low risk of malignant transformation, the plexiform type is pathognomonic for neurofibromatosis type 1 (NF 1) and carries an increased risk of malignant transformation.
- Complete excision of the lesion is curative.

SCHWANNOMA

- Schwannomas are benign tumours of the nerve sheath that grow slowly and push nerve fibers aside. They occur most often as solitary tumour but on occasion as multiple lesions.
- Schwannomas can arise from any peripheral nerve containing Schwann cells, including cranial nerves. (The sheath surrounding nerve cells outside the central nervous system is made up of Schwann cells. They are important to nerve regeneration.)
- The eighth cranial nerve is the most susceptible to schwannomas. Bilateral schwannomas of the eighth cranial nerve indicate the presence of type 2 neurofibromatosis, which is a genetic condition.
- In most cases the cause of a schwannoma is unknown, although radiation is suspect on occasion.

SCHWANNOMA

- Mild nerve function problems or pain caused by pressure on the surrounding nerve are the usual symptoms.
- Schwannomas within the spinal canal may assume a dumbbell shape that extends into or out of the spinal canal along a nerve root. Compression of the spinal cord can lead to weakness, numbness, stiffness, trouble controlling urine or bowel, and paralysis.
- Compression of the nerve root can lead to pain shooting down the arms or legs, weakness or numbness.

SCHWANNOMA

- Schwannomas with symptoms are surgically removed. Some surgeons advocate removing asymptomatic lesions because they often will grow.
- In most cases surgical removal involves little or no injury to the parent nerve. Recurrences after total removal are rare.

PERINEURIOMA

- Uncommon benign tumour of peripheral nerve composed primarily of perineurial cells.
- They have been traditionally classified into two main types according to their location—intraneural and extraneural—and overlap histologically with many other tumours, which may be diagnostically challenging to general surgical pathologists.
- Intraneural perineurioma affects commonly young adults, equally males and females.
- Patients typically present with equal distribution between upper and lower limbs with gradual onset of a motor-predominant neuropathy which may accompanied with a mild sensory component.
- The pathological examination of perineurioma has demonstrated a distinctive nerve lesion.
- The perineurial tumour is composed of concentric layers of perineurial cells. These concentric layers of cells resemble the onion-bulb appearance in Schwann cell lesions. However the Schwann cell lesions arise from endoneurial layers and perineurioma arise from perineurial layer which made the term pseudo-onion bulb lesion more suitable and acceptable for the perineuriomas.
- The immunohistochemical staining can help to distinguish between perineurioma and Schwann cell lesion as the first is positive for epithelial membrane antigen (EMA) and negative for (s-100) and the Schwann cell lesions demonstrate the opposite pattern.

PERINEURIOMA

- Some genetic abnormalities in perineurioma have been linked to the long arm of chromosome 22, known to contain the abnormalities in schwannoma and neurofibromatosis .
- This tumour should be suspected for any slow progression motor deficit with or without sensory components, with focal hyperintense lesion on T2-weighted MRI images.
- Extremities and trunk most common sites
- Cause progressive debilitating focal extremity weakness, that does not recur or metastasize.
- The surgical decision should be taken in relation with patient age and functional deficit.

HYBRID NERVE SHEATH TUMOUR

- Hybrid peripheral nerve sheath tumours (PNSTs) have been recognized recently and were first included in the 4th edition of World Health Organization (WHO) Classification of Tumours of Soft tissue and Bone, published in 2013.
- These tumours show combined features of more than one type of conventional benign peripheral nerve sheath tumours.
- The most common combinations are those of schwannoma/perineurioma followed by combinations of neurofibroma/schwannoma and neurofibroma/perineurioma.
- Hybrid PNSTs are distinct tumours and are usually benign. However, rare case reports have described local recurrence and at least two recent case reports have described malignant transformation in these tumours.

DERMAL NERVE SHEATH MYXOMA

- Nerve sheath myxoma is an uncommon benign neoplasm with nerve sheath like features.
- It has several cytological and histological differential diagnoses. One such lesion is neurothekeoma, which can be differentiated using immunohistochemistry.
- The nerve sheath myxomas and myxoid neurothekeomas which were considered synonymous in the past can be distinguished by use of immunohistochemical marker S100, which is positive for nerve sheath myxoma and negative for neurothekeoma. This differentiation may be important clinically as nerve sheath myxomas have higher propensity to cause local recurrences.

GANGLIONEUROMA

- Neuroblastic tumours are the most common extra-cranial solid tumours in childhood and include neuroblastoma, ganglioneuroblastoma (nodular or intermixed), and ganglioneuroma.
- They arise from the neural crest and range from immature, undifferentiated to mature, differentiated tumours.
- According to the International Neuroblastoma Pathology Classification (INPC), ganglioneuroblastoma intermixed (GNBI) and ganglioneuroma (GN) represent the mature end of this range. In this system, GN maturing has been defined as a “link” between GN and GNBI.
- Ganglioneuroma has been first described more than 150 years ago. A variety of case reports on GN have been published, ranging from patients with symptoms due to huge tumor masses to speculations about malignant transformation and dedifferentiation into neuroblastoma.
- Surgery is often performed due to clinical symptoms and/or theoretical concerns that GN may transform into neuroblastoma (NB);
- GN and GNB-I have a slow growth rate and resection can be associated with significant morbidity. Watch and wait approaches should be considered for some GN and GNB-I.

HEMANGIOBLASTOMA

- Hemangioblastomas are uncommon vascular tumours of the central nervous system.
- They account for less than 3% of all central nervous system tumours and are generally benign, well-circumscribed but highly vascular, neoplasms.
- They mostly occur in infratentorial structures such as the cerebellum, the brainstem, and the spinal cord.
- Approximately 5% of all spinal cord tumours and 7.5% of all tumours arising in the adult posterior fossa are accounted to be a hemangioblastoma.
- Symptomatology occurs by local compression of neural structures and rarely because of bleeding or as a paraneoplastic complication.

HEMANGIOBLASTOMA

- Diagnosis is suspected by gadolinium-enhanced magnetic resonance imaging (MRI). The characteristic MRI feature is a contrast enhancing nodule associated with a peritumoral cyst located in the cerebellum or a homogeneously enhancing lesion on the surface of or within the spinal cord with an associated syrinx. These lesions appear as a low signal on T1-weighted images and as a high signal on T2-weighted sequences.
- These features, however, are not pathognomonic, so the definitive diagnosis is made on histopathological examination. Microscopic investigation shows an extensive vascular network with neoplastic stromal cells. The neoplastic stromal cells have abundant cytoplasm with lipid vacuoles resulting in a typical clear cell morphology. Nuclear hyperchromatism and atypia, in contrast to absence of mitotic activity, are a very typical pattern of hemangioblastomas.

SPORADIC HEMANGIOBLASTOMA

- Hemangioblastomas do not have a gender predisposition.
- They can occur either sporadically or as a component in Von Hippel Lindau syndrome.
- Approximately 75% of all hemangioblastomas are sporadic.
- The average age at presentation of a sporadic hemangioblastoma is in the fourth and fifth decade of life. Sporadic hemangioblastomas are, in general, solitary.
- Surgical resection can offer definitive therapy in sporadic hemangioblastomas. A complete surgical resection is usually feasible and the lesion normally does not reoccur.
- When tumor localization is invading vital structures and a tumor progression or neurological deficit is observed, operative intervention should be considered. As such, in 82-98% of cases, symptoms will improve or stabilize. Stereotactic radiosurgery or conventional radiation therapy can be considered in case of an inoperable lesion.

HEMANGIOBLASTOMA ASSOCIATED WITH VHLD

- Hemangioblastomas associated with VHLD are generally diagnosed at a younger age, in the second and third decade of life.
- They usually are multiple.
- While a complete surgical resection usually provides a definitive cure in sporadic hemangioblastomas, VHL associated hemangioblastomas tend to recur. Therefore therapeutic measure should focus on careful timing of surgical intervention(s).
- Surgical intervention should be reserved for symptomatic lesions, lesions with a demonstrated accelerated growth pattern or lesions that would compromise important neurological structures in the near future.
- Stereotactic gamma knife radiosurgery and radiation therapy may play a role in avoiding multiple neurosurgical interventions or in lesions that are not accessible by surgery.

➤ MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS

- A malignant peripheral nerve sheath tumor (MPNST) is a tumor that develops in the protective lining that covers nerves.
- The first symptom of MPNST is often a lump or mass that increases in size, sometimes causing pain or a tingling sensation.
- Treatment of MPNST begins with surgery to remove as much of the tumor as possible and may or may not be followed by radiation therapy to decrease the chance of a recurrence.
- Chemotherapy might be used if the whole tumor cannot be removed during surgery or to treat a metastasis.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS

- These tumours account for up to 10% of all soft tissue sarcomas and are associated with poor prognosis unless wide excision of the tumor is undertaken before local invasion or distant metastasis can occur.
- The incidence of sporadic MPNST is low, with a lifetime risk of 0.001%, but in association with the familial condition NF1, where these tumours often arise from malignant transformation of a plexiform neurofibroma, the incidence is much higher. Evans *et al.* estimated the lifetime risk of developing MPNST in the population of patients with NF1 to be as high as 13%.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS

- Due to the relative rarity of MPNST, there have been few large studies into survival.
- Patient presented with tumor size >5 cm, tumor location at the head or neck, strong family history of NF1, recurrent or distant metastatic, and increase Ki-67 has poor prognosis.