Peripheral Nerve Tumors

Laszlo L. Mechtler

Introduction

Peripheral nerve tumors are located on cranial nerves, spinal nerve roots, peripheral nerves, and the sympathetic chain. The cells of origin are neurons or nerve sheath cells. Tumors of neuronal origin, whether central or peripheral, are rare. Tumors of nerve sheath origin are composed of Schwann cells, perineural cells, or fibroblasts. The Schwann cell, like oligodendroglia in the central nervous system, forms myelin sheaths. It originates from the neural crest, as do sensory and autonomic neurons, meningocytes, melanocytes, chromaffin cells, and perineural cells. The endoneurium is the content of the nerve fascicles, comprising the connective tissue of the nerve fascicle, the individual nerve fibers with their Schwann cell sheaths, and the endoneurial capillaries. The smallest connective tissue unit of the nerve is the endoneurium, which encircles individual nerve fibers. The Schwann cell is the innermost component of the endoneurium; other components are capillaries, collagen fibers, and fibroblasts. The endoneurium is surrounded by the perineurium, which is composed of flattened specialized cells, each with a basal lamina. This perineurial layer is in direct continuity with the pia-arachnoid. The epineurium is the outermost sheath of the nerve, and it encompasses several nerve fascicles. The gross anatomical structure is recognized as the nerve, including blood vessels and connective tissue that are mesodermal in origin (Figure 58E.1).

FIGURE 58E.1

A cross-sectional diagram of a peripheral nerve demonstrating the endoneurium, which contains the neural elements. Bundles of nerve fibers are bound by the perineurium to form fascicles. The epineurium surrounds and lies between the fascicles and forms a barrier, creating an endoneurial microenvironment.
Electron microscopy and immunohistochemistry are necessary for accurate diagnosis of peripheral nerve tumors. S-100 protein, Leu-7, myelin basic protein, and glial fibrillary acidic protein are immunohistochemical markers of Schwann cells. Perineural cells stain with antibodies that react to the epithelial membrane antigen but not to the S-100 protein, and they function as a diffusion barrier. Schwann cells and perineural cells have basal laminae that are absent in fibroblasts. Schwann cells probably synthesize their basal laminae. Immunohistochemical staining and ultrastructural findings are most helpful in differentiating malignant peripheral nerve sheath tumors (MPNSTs) from other soft tissue sarcomas, such as fibrosarcomas, synovial sarcomas, and leiomyosarcomas.

The World Health Organization classifies anaplastic peripheral nerve tumors as MPNSTs instead of individually referring to neurogenic sarcomas, anaplastic neurofibromas, or malignant schwannomas (Wanebo et al. 1993). Schwannomas and neurofibromas are the most common benign peripheral nerve tumors. The Schwann cell is thought to be the cell of origin in both. Other benign peripheral nerve growths are hamartomas, cysts, and neuromas (Table 58E.1).

**Table 58E.1**

**Tumorlike conditions of the peripheral nerves**

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morton’s neuroma (plantar neuroma)</td>
<td>Fibrosing process of plantar digital nerve with pain between the third and fourth metatarsals</td>
</tr>
<tr>
<td>Amputation neuroma</td>
<td>Disorganized proliferation of a proximal nerve after transection; tender to pressure</td>
</tr>
<tr>
<td>Nerve sheath ganglion (nerve cyst)</td>
<td>Mucin-filled cyst in perineurium; most commonly seen affecting the peroneal nerve</td>
</tr>
<tr>
<td>Neuromuscular hamartoma (benign bundles; rare triton tumor)</td>
<td>Mosaic tumor with mature striated muscle intermingled within nerve</td>
</tr>
<tr>
<td>Mucosal neuroma</td>
<td>Nodular thickening of lips, tongue, and eyelids of patients associated with type 2b multiple endocrine neoplasia</td>
</tr>
</tbody>
</table>

**Source:** Modified from JM Woodruff. The pathology and treatment of peripheral nerve tumors and tumor-like conditions. CA Cancer J Clin 1993;43:290–308.
Schwannomas

Schwannomas account for 8% of all intracranial primary tumors in adults. Eighty percent to 90% of those occur in the cerebellopontine angle. They are also the most common spinal nerve tumor. Previously, schwannomas were described as either neurilemomas or neurinomas, although schwannoma is now the preferred terminology. The salient feature of neurofibromatosis type 2 (NF-2) is the vestibular schwannoma that occurs bilaterally in more than 95% of patients. Two-thirds of patients with NF-2 develop spinal or subcutaneous schwannomas, which may precede the development of vestibular schwannomas. Schwannomatosis is the term used to describe multiple schwannomas without evidence of NF-1 or NF-2 (MacCollin et al. 1996).

Histology
Schwannomas are benign encapsulated tumors with two characteristic components: a highly cellular type (Antoni type A) and a loose myxoid type (Antoni type B). Degenerative changes are prominent in large tumors and in deep locations, such as the retroperitoneum. These changes include cyst formation, calcification, hemorrhage, and hyalinization. Schwannomas are immunoreactive for S-100 protein and to a lesser degree for Leu-7 (Figure 58E.2).

FIGURE 58E.2

Classic schwannoma, composed of compact interwoven bundles of bipolar spindle cells. Note palisading. (Courtesy of RR Heffner, State University of New York, Albany.)

Clinical Features
Schwannomas have a predilection for flexor surfaces of the limbs and main nerve trunks. The age at presentation is 20–50 years. They are almost always solitary and arise eccentrically from within the nerve; therefore, nerve bundles are stretched over the surface of the tumor. Weakness and
sensory symptoms are unusual unless the tumor is in a confined space, such as the carpal tunnel. The initial symptom is usually a painful swelling, although deep-seated tumors, especially those in the mediastinum, may grow very large before detection.

The most characteristic diagnostic feature is shooting pain and paresthesias induced by palpation of the nerve. Spontaneous pain is unusual. About 10% of schwannomas are predominantly Antoni type A and are designated cellular schwannomas. These are misinterpreted as malignant because of hypercellularity, hyperchromasia, and abundant mitoses in 30% of cases. Despite these features, the tumor is benign and forms a painless mass, usually in the paravertebral region of the retroperitoneum, pelvis, and mediastinum.

Plexiform or multinodular schwannomas comprise 5% of the total and occur predominantly in the subcutaneous tissue of young adults. These are also benign. Melanotic schwannomas are the rarest form of schwannoma. They originate from Schwann cells that are capable of melanogenesis and involve the nerve roots. Melanotic schwannomas are also benign but are associated with cardiac myxomas, which are the main cause of morbidity.

**Diagnosis**

Magnetic resonance imaging is the most specific study for evaluating peripheral nerve sheath tumors. Schwannomas are hyperintense on T2-weighted images and isointense with muscle on T1-weighted images. Schwannomas tend to be situated at the periphery of the nerve. The development of magnetic resonance neurography has enhanced both the resolution and conspicuousness of the peripheral nerve and surrounding structures. In NF-1, two-thirds of patients can undergo complete excision of a neurofibroma, with a small percentage requiring graft repair at nerves (Donner et al. 1994). Magnetic resonance neurography is useful in assessing the resectability of neurofibromas preoperatively (Kuntz et al. 1996) (Figure 58E.3).
Neurofibroma consisting of a mixture of proliferated Schwann cells and fibroblasts between dispersed nerve fibers. (Courtesy of RR Heffner, State University of New York, Albany.)

**Treatment**
The goals of treatment are tumor resection with preservation of nerve function. Malignant transformation does not occur, and even after partial resection, most patients do not experience symptomatic regrowth. Nerve function may be monitored intraoperatively by intermittently measuring nerve action potentials. Large, histologically benign schwannomas (classic, cellular, plexiform, and melanotic) should not be totally excised if removal would cause neurological deficits.

**Neurofibromas**

In 90% of cases, neurofibromas are solitary tumors. The age of onset is 20–30 years. Multiple tumors are seen in people with NF.

**Histology**
Neurofibromas have fewer Schwann cells and more collagen and reticulin fibers than schwannomas do (see Figure 58E.3). Myelinated and unmyelinated axons are characteristically included in the substance of the tumor. Tumor cells are immunoreactive for S-100 protein but not for epithelial membrane antigen.

**Clinical Features**
Solitary neurofibromas are located predominantly on cutaneous nerves. Patients may complain of painful swelling, but palpation of a mass does not reproduce the shooting pain and paresthesias characteristic of schwannomas. Neurofibromas more often cause weakness and sensory symptoms when noncutaneous sites are involved. Malignant transformation of solitary neurofibromas is rare.

NF is a complex disorder that affects both the neuroectoderm and mesoderm (see Chapter 69). NF-1 is subclassified into three groups: (1) multiple neurofibromas, which are usually large and involve deep and major nerves; (2) plexiform neurofibromas, which form solitary, tortuous, fusiform enlargements of nerves; and (3) diffuse neurofibromas, seen in children and young adults, forming a subcutaneous or cutaneous plaquelike elevation of the skin. NF-2 is characterized by bilateral acoustic schwannomas, peripheral neurofibromas, meningiomas, and gliomas.
Diagnosis
Magnetic resonance imaging distinguishes neurofibromas from schwannomas (Table 58E.2). Although both tumors are hyperintense on T2-weighted images and isointense with muscle on T1-weighted images, two-thirds of neurofibromas showed a target pattern of increased peripheral signal intensity and decreased central signal intensity on T2-weighted studies. Unlike schwannomas, neurofibromas are in a central position and may not be distinguishable from the nerve.

Table 58E.2
Comparison of schwannomas and neurofibromas

<table>
<thead>
<tr>
<th></th>
<th>Schwannoma</th>
<th>Neurofibroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age</td>
<td>20-50 yrs</td>
<td>20-30 yrs, younger in NF</td>
</tr>
<tr>
<td>Gross appearance</td>
<td>Encapsulated, rarely plexiform</td>
<td>Nonencapsulated, more often plexiform</td>
</tr>
<tr>
<td>Cut surface</td>
<td>Tan-brown; may be cystic hemorrhagic</td>
<td>Homogeneous gray and gelatinous</td>
</tr>
<tr>
<td>S-100 immunostaining</td>
<td>Staining relatively uniform and intense</td>
<td>Staining variable</td>
</tr>
<tr>
<td>Relation to NF-1</td>
<td>Uncommon</td>
<td>Predominant type</td>
</tr>
<tr>
<td>Malignant</td>
<td>Almost never</td>
<td>Rare in solitary form; 4% in NF-1</td>
</tr>
<tr>
<td>transformation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>Palpation produces pain and paresthesias; motor/sensory deficits uncommon</td>
<td>Palpation does not commonly produce pain or paresthesias; motor/sensory deficits prominent</td>
</tr>
</tbody>
</table>

NF = neurofibromatosis.

Malignant Peripheral Nerve Sheath Tumors

Most neuropathologists believe that MPNSTs arise from the Schwann cell (malignant schwannoma) but prefer the term MPNST because it is noncommittal in defining the cell of origin. The prevalence of MPNSTs is 0.001% in the general population and 4% in patients with NF. NF accounts for approximately 50% of MPNSTs (Wanebo et al. 1993). These usually arise from transformed solitary neurofibromas or plexiform neurofibromas.
Irradiation of neurofibromas has also been implicated in malignant transformation.

**Histology**

MPNSTs arise as large fusiform or eccentric masses, which suggests that tumor spreads both proximally and distally along the nerve sheath. The average size at diagnosis is 5 cm. Unlike benign nerve sheath tumors, 50% of MPNSTs show large areas of necrosis. The characteristic histology is hypermitotic, densely packed, polychromatic, interlacing spindle cells with slender or curved nuclei and indistinct cytoplasm. One-half of the cells express S-100 protein (Figure 58E.4). Schwann cells, because of their origin in the neural crest, retain the capacity to differentiate into other cell types. This divergent differentiation occurs in 15–28% of MPNSTs.

![FIGURE 58E.4](image)

Malignant peripheral nerve sheath tumors showing pleomorphic, densely packed cells, generally configured in parallel bundles. (Courtesy of RR Heffner, State University of New York, Albany.)

Peripheral nerve sheath tumors with foci of rhabdomyosarcoma are called *malignant triton tumors*. Mature islands of cartilage and bone are common elements, but mucin-secreting glands are rare in these tumors.

**Clinical Features**

MPNSTs cause spontaneous pain, swelling, and marked motor and sensory disturbances. The swelling is firm and immovable. MPNSTs should be suspected in patients with NF-1 who experience rapid increases in size of neurofibromas, especially when associated with pain and new neurological disturbances. The sciatic nerve is the one most often involved, followed by tumors of the brachial plexus and sacral plexus (Figure 58E.5).

![FIGURE 58E.5](image)
A noncontrast T1-weighted sagittal image shows an eccentric, ball-like enlargement of the sciatic nerve displacing the nerve trunk posteriorly.

Treatment

MPNSTs are highly malignant tumors with a propensity for recurrence (at a rate of 45%) and metastasis, usually to the lung, liver, or bone. Median survival time from diagnosis is about 3 years. The 5-year survival rate is 34–39%. Surgical resection is the most effective treatment, usually requiring amputation of the limb or wide en bloc excision followed by adjuvant radiation therapy. Chemotherapy is ineffective. Prognosis is adversely affected by a large tumor (>5 cm), presence of NF-1, and a centrally located tumor (Hajdu 1993)

**Primary peripheral nerve sheath tumors**

**Schwannoma** (neurilemoma)
- Classic
- Cellular
- Plexiform
- Melanotic

**Neurofibroma**
- Solitary
- Multiple
- Plexiform
- Diffuse

**Malignant peripheral nerve sheath tumor**
- Malignant triton tumors
- Glandular malignant schwannoma
- Malignant epithelioid schwannoma


Classification of Cranial Neuropathies
Neoplastic: Carcinoma, lymphoma, leukemia, glioma, myeloma

infection: Tuberculosis, syphilis, leprosy, mycoplasma, Lyme disease, viral infections, fungal infections, parasitic infections

Postinfectious and demyelinating: Bell's palsy, Ramsay Hunt syndrome, ophthalmoplegic migraine, Miller Fisher syndrome, polyneuritides, multiple sclerosis

Granulomatosis: Sarcoidosis, idiopathic granulomatosis, vasculitis, inflammatory granulomatosis

Angiopathic: Wegener's granulomatosis, Churg-Strauss syndrome, Behçet's syndrome, diabetes

Idiopathic: Idiopathic pachymeningitis, Tolosa-Hunt syndrome

Physical or chemical: Radiation, trauma, surgery, toxins, drugs
Hereditary: Dejerine-Sottas disease, Krabbe's disease

Primary nerve tumors: Schwannoma, neurofibromatosis