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Ultrasound and MR imaging of peripheral nerve tumors: the state of the art

Guillaume Lefebvre¹ · Thomas Le Corroller^{2,3}

Abstract

Peripheral nerve sheath tumors are a heterogeneous subgroup of soft tissue tumors that either arise from a peripheral nerve or show nerve sheath differentiation. On imaging, direct continuity with a neural structure or location along a typical nerve distribution represents the most important signs to suggest the diagnosis. Ultrasound and magnetic resonance imaging are the best modalities to evaluate these lesions. First, it is necessary to differentiate between a true tumor and a non-neoplastic nerve condition such as a neuroma, peripheral nerve ganglion, intraneural venous malformation, lipomatosis of nerve, or nerve focal hypertrophy. Then, with a combination of clinical features, conventional and advanced imaging appearances, it is usually possible to characterize neurogenic tumors confidently. This article reviews the features of benign and malignant peripheral nerve sheath tumors, including the rare and recently described tumor types. Furthermore, other malignant neoplasms of peripheral nerves as well as non-neoplastic conditions that can mimic neurogenic tumor are herein discussed.

Keywords Nerve · Peripheral nerve sheath tumor · MR imaging · Ultrasound

Key points

- On imaging, direct continuity with a neural structure, location along a typical nerve distribution, fusiform shape, split-fat sign, target sign, and fascicular appearance suggest the diagnosis of peripheral nerve tumor.
- Intraneural perineurioma is an underdiagnosed benign nerve neoplasm that affects children and young adults, and presents characteristic imaging features.
- In the setting of type 1 neurofibromatosis, malignant peripheral nerve sheath tumor must be suspected in case of a distinct growing mass on MR imaging or increased activity on PET.
- Non-neurogenic neoplasms of peripheral nerves (synovial sarcoma, neurolymphoma, and metastatic disease) can mimic peripheral nerve sheath tumor on imaging, and should therefore be included in the differential diagnosis.

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Introduction

Peripheral nerve sheath tumors (PNSTs) are a heterogeneous subgroup of soft tissue tumors that either arise from a peripheral nerve or whose component cells show evidence of nerve sheath cell differentiation [1]. In the fifth edition of the World Health Organization (WHO) classification, the PNST group includes benign and malignant tumors listed in Table 1 [2]. Benign and malignant PNSTs can occur sporadically as well as in conjunction with neurocutaneous syndromes, including neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis. PNSTs represent overall a significant percentage of all soft tissue tumors, accounting for approximately 12% of all benign and 8% of all malignant soft tissue neoplasms [3–5]. Benign neurogenic tumors are by far more common than malignant ones, with schwannoma and neurofibroma representing the most frequent tumor types in this group [3]. On the other hand, malignant PNST is an aggressive entity with a high rate of local recurrence and distant metastasis [4]. Besides, other malignancies may involve peripheral nerves, including metastatic disease, neurolymphoma, and synovial sarcoma [6].

The diagnosis of a neurogenic tumor is based on a combination of clinical features, anatomical location of the lesion,

Table 1 World Health Organization (WHO) classification of peripheral nerve sheath tumors

Benign	Malignant
Schwannoma (including variants)	Malignant PNST
Neurofibroma (including variants)	Malignant PNST epithelioid
Perineurioma	Malignant melanotic nerve sheath tumor
Granular cell tumor	Malignant granular cell tumor
Nerve sheath myxoma	Malignant perineurioma
Solitary circumscribed neuroma	
Ectopic meningioma	
Neuromuscular choristoma (triton tumor)	
Hybrid nerve sheath tumor	

and imaging appearances. In most centers, ultrasound (US) and magnetic resonance (MR) imaging are routinely used to study peripheral nerves. US offers high-resolution imaging and can easily demonstrate direct continuity of the tumor with a neural structure [7]. In addition, when the lesion is indeterminate, US can be used to guide biopsy and provides in this setting excellent fascicle visualization to minimize the risk of nerve damage [7]. On the other hand, MR imaging remains the gold standard for soft tissue tumor evaluation and presurgical planning [5]. It is especially well suited for deeper lesions and in patients with a high body mass index. Furthermore, MR imaging can even be used as a screening tool in individuals with NF1, allowing early diagnosis of malignant degeneration in preexisting PNST [8, 9].

This article aims at reviewing the features of benign and malignant PNSTs, including the rare and most recently described tumor types, on high-resolution US as well as on conventional and advanced MR imaging. In addition, other neoplasms of peripheral nerves as well as non-neoplastic conditions that can mimic neurogenic tumors will herein be discussed and illustrated.

Schwannoma

Schwannoma is a benign PNST composed of differentiated neoplastic Schwann cells [10]. Schwannomas account for approximately 5.2% of all benign soft tissue tumors, with most lesions being solitary and sporadic [3]. It can affect all ages but presents a peak incidence in the third to sixth decades of life [11]. The tumor is generally slow-growing, and may either present as an asymptomatic mass or be painful. It frequently affects peripheral nerves along the flexor surfaces of the upper and lower extremities as well as in the skin and subcutaneous tissues of the head and neck [12, 13]. Spinal intradural extramedullary sites and cranial nerve involvement are also common [11]. In contrast, intraosseous schwannoma is exceedingly rare with reported locations in the mandible, maxilla, petrous apex, and long bones of the extremities [14].

Multiple schwannomas are a feature of NF2 and schwannomatosis [11]. NF2 can either be inherited in an autosomal dominant manner or related to new sporadic mutations. Schwannomas characteristically occur before the age of 30, with bilateral vestibular schwannoma being pathognomonic of NF2 [11]. NF2 patients may also present with meningiomas and gliomas. In contrast, schwannomatosis is characterized by the presence of multiple schwannomas that manifest later in adulthood, in the absence of vestibular nerve involvement and meningiomas [11].

Histologically, conventional schwannoma is an encapsulated spindle cell tumor composed of well-differentiated Schwann cells [11]. Schwannoma may demonstrate various morphological appearances. Most often, it presents as a biphasic tumor with compact areas (Antoni A tissue) alternating with loosely arranged foci (Antoni B tissue). Diffuse staining for S100 in cell nuclei and cytoplasm, more prominent in Antoni A areas, is constantly demonstrated as well as extensive SOX10 immunoreactivity [11]. Specific morphological subtypes may deviate from the description above. Ancient schwannoma differs by the presence of scattered bizarre-appearing nuclei, and may exhibit extensive hyalinization and central ischemic changes. Cellular schwannoma is composed predominantly or exclusively of Antoni A tissue, and may be encountered at paravertebral sites, mediastinum, retroperitoneum, and pelvis. Plexiform schwannoma differs from the conventional schwannoma by its absence of a well-formed capsule and by its multinodular shape. It may either occur sporadically or be reported in patients with NF2 or schwannomatosis [15]. Epithelioid schwannoma characterized by multilobulated growth of epithelioid cells associated with conventional areas of Antoni A or Antoni B tissue can in the same way be observed either sporadically or in the setting of schwannomatosis [16]. Finally, microcystic or reticular schwannoma is the rarest subtype of schwannoma and occurs preferentially in visceral sites [17].

On US, schwannoma typically appears round or oval, hypoechoic, and with well-defined margins, and can exhibit slight posterior acoustic enhancement (Fig. 1). In most cases, the tumor demonstrates continuity with the nerve at

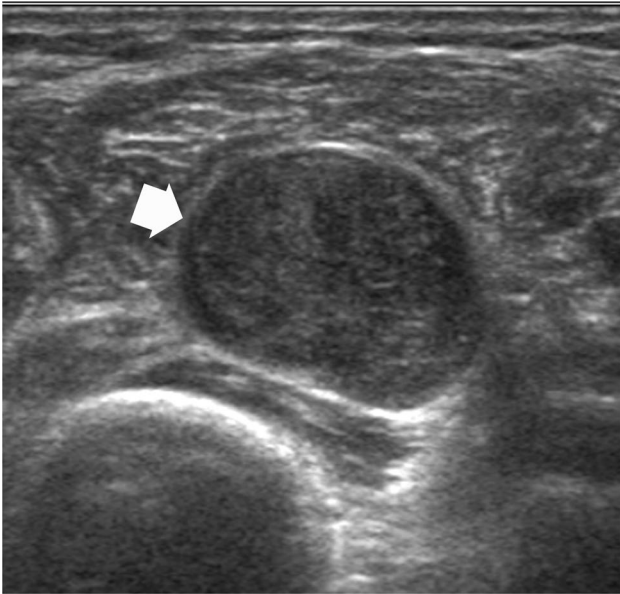


Fig. 1 Schwannoma. Short-axis US image over the radial nerve in the arm demonstrates a round and hypoechoic mass (thick arrow), with well-defined margins and posterior acoustic enhancement

its proximal and distal poles. Furthermore, with the development of high-frequency probes, high-resolution US can sometimes demonstrate a connection of the schwannoma with a swollen fascicle whereas the unaffected fascicles appear displaced at the periphery [7]. In contrast, the role of advanced US techniques such as elastography and contrast needs further evaluation for the diagnosis of PNST [18].

On MR imaging, schwannoma is classically round or fusiform in shape, less than 5 cm in size, and appears isointense or slightly hyperintense to skeletal muscle on T1-weighted images and markedly hyperintense to fat on T2-weighted images (Fig. 2). Most importantly, schwannoma often exhibits characteristic MR imaging features that indicate its neurogenic origin (Table 2). First, the *tail sign* is pathognomonic for PNSTs and refers to the visualization of the involved nerve entering and/or exiting the neoplasm (Fig. 2). This sign is observed when a PNST affects large peripheral nerves, but may be impossible to assess in small or superficial lesions. In fact, fewer than half of schwannomas demonstrate an evident attached nerve and appear encapsulated within the epineurium [12]. In this situation, the eccentric and separate relationship of schwannoma relative to the involved nerve is crucial to distinguish it from neurofibroma. The *fascicular sign* is another finding suggestive of PNST, that describes multiple ring-like hypointense structures with peripheral hyperintensity on transverse T2-weighted images, reflecting the enlarged fascicles surrounded by the perineurium [5, 19]. In addition, a thin hypointense capsule may be identified on T2-weighted images [19]. The *split-fat sign* is not specific for PNST, but indicates a tumor origin

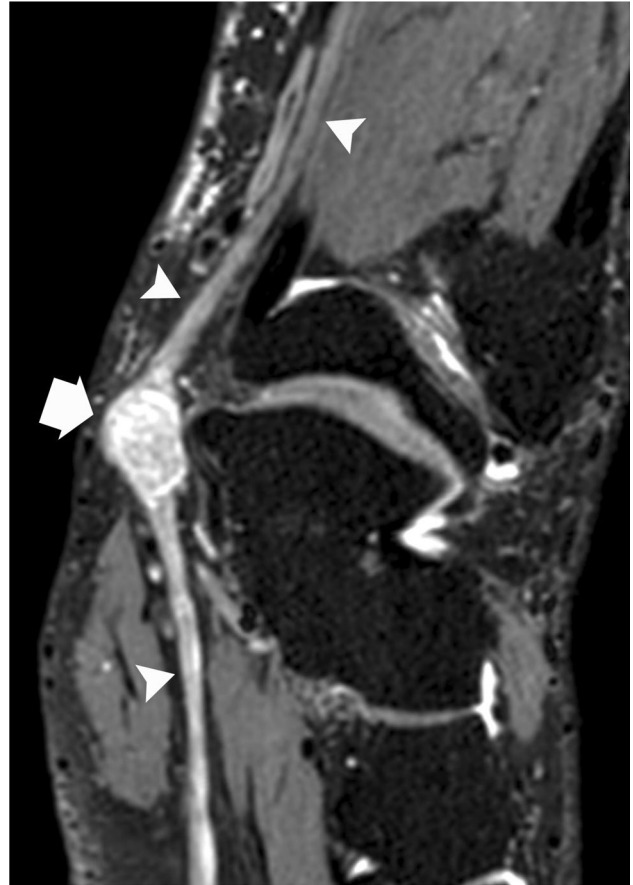


Fig. 2 Schwannoma. Oblique sagittal fat-suppressed T2-weighted MR image exhibiting a small and well-defined mass (thick arrow) arising from the medial plantar nerve. Note the typical *tail sign* with visualization of the involved nerve entering and exiting the neoplasm (arrowheads)

in the intermuscular space with a rim of fat best depicted on T1-weighted images about neurogenic neoplasms. The *target sign* is highly suggestive of PNST [19]. It consists of transverse T2-weighted images of central low or intermediate signal intensity surrounded by a rim of higher signal intensity (Fig. 3). This characteristic MR pattern reflects the histological features of the tumor with a fibrocollagenous core surrounded by peripheral myxomatous tissue. Rarely, a reverse target appearance can be observed on T1-weighted MR images with central hyperintensity and peripheral hypointensity [19]. On contrast-enhanced images, schwannomas classically show diffuse enhancement, except for large tumors that demonstrate predominantly peripheral or inhomogeneous enhancement (Fig. 4) [12].

Specific schwannoma subtypes may present distinct imaging features from conventional schwannoma. First, intralesional calcification can be encountered in the “ancient” variant of schwannoma as well as in epithelioid schwannoma [20]. Second, because degenerative change

Table 2 Imaging features that may help in differentiation between schwannoma and neurofibroma

	Schwannoma	Neurofibroma
Situation in the nerve	Eccentric	Central
Target sign	+	+++
Fascicular sign	++	+
Cystic changes	++	±
Calcifications	+	-
Enhancement	Diffuse or peripheric	Central or diffuse
DWI (ADC)	$1.5 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$	$1.8 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$
Tractography	Preserved or partially disrupted nerve tracts	Partially disrupted nerve tracts

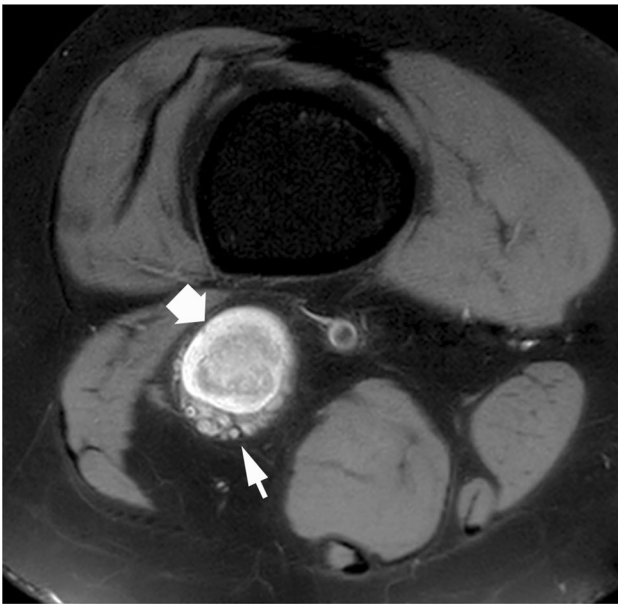


Fig. 3 Schwannoma. Axial water-only T2-weighted DIXON MR image in a patient with neurofibromatosis type 2 demonstrating a round and well-defined mass (thick arrow), involving the origin of the tibial nerve. The lesion is of high-signal intensity peripherally and low-signal centrally (*target sign*). Note that the unaffected nerve fascicles are displaced at the periphery (thin arrow)

with hemorrhage and cyst formation cause extensive signal heterogeneity, the target sign is generally absent in ancient or large schwannomas (Fig. 4). In the same way, plexiform schwannoma, when it occurs in the deep soft tissues, can present as a multinodular inhomogeneous mass without a target sign [21]. Finally, at paravertebral sites, extensive bone erosion, extension into the vertebral canal, and compression of spinal roots can be observed in cellular schwannoma which may lead to an erroneous diagnosis of malignancy [22].

Advanced MR imaging techniques may be useful for neurogenic tumor characterization [8]. MR neurography can demonstrate preoperatively the prominent nerve fascicles affected by schwannoma and help identify the uninvolved fascicles splayed about the tumor [23, 24]. On diffusion-weighted imaging (DWI), schwannoma demonstrates significantly lower apparent diffusion coefficient (ADC) values ($1.5 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$) than neurofibroma ($1.8 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$) (Fig. 5) [25]. Moreover, diffusion tensor imaging (DTI) with fiber tractography may allow to preoperatively describe the tumor location in relation to the nerve fascicles and to accurately differentiate between schwannoma and neurofibroma [24, 25].

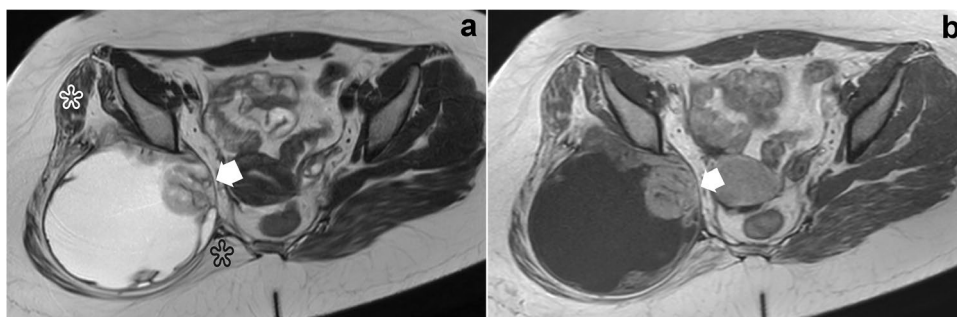


Fig. 4 Schwannoma with cystic degeneration. Axial T2-weighted (a) and corresponding contrast-enhanced T1-weighted (b) MR images showing a large cystic mass affecting the sciatic nerve (thick arrow),

with fatty atrophy of the gluteal muscles (asterisks). Note that the tumor presents a peripheral enhancement pattern after contrast injection

Fig. 5 Schwannoma. Axial post-contrast water-only T1-weighted DIXON MR image (a) showing a large, eccentric, and multilobulated sacral mass (thick arrow) demonstrating intense and slightly heterogeneous enhancement. On the corresponding axial B800 diffusion-weighted MR image (b), the lesion exhibits restricted diffusion (thick arrow) with a subtle targetoid appearance

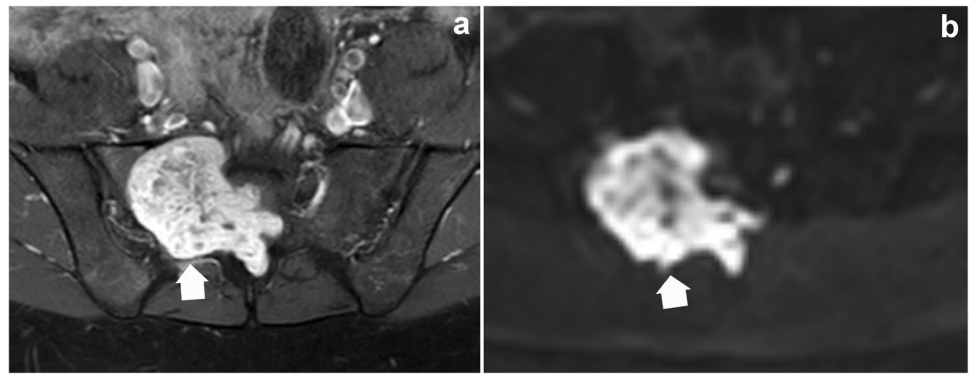


Table 3 Spectrum of neurofibromatosis type 1-associated nerve sheath tumors

Diagnosis	Histological features
Neurofibroma	No atypia
Plexiform neurofibroma	Diffusely enlarging and replacing a nerve
Neurofibroma with atypia	Cytological atypia
Cellular neurofibroma	Hypercellularity
ANNUBP	Cytological atypia, hypercellularity, loss of architecture, < 1.5 mitoses/mm ²
MPNST	Features of ANNUBP with > 1.5 mitoses/mm ² , \pm necrosis

Neurofibroma

Neurofibroma is characterized by neoplastic Schwann cells immersed in a variably loose myxoid stroma associated with other cell components including perineurial and stromal cells [26]. Neurofibromas account for approximately 5.3% of all benign soft tissue tumors, and may either occur sporadically as solitary lesions, or less often be encountered as multiple tumors in individuals with NF1 [3]. The skin is the most common site of involvement with cutaneous neurofibromas presenting as asymptomatic mobile soft lesions. Less often, neurofibroma affects a major nerve trunk or nerve plexus, and presents with sensory or motor symptoms in the distribution of the affected nerve [26]. Macroscopically, five appearances can be encountered: localized cutaneous, diffuse cutaneous, localized intraneural, plexiform intraneural, and diffuse neurofibroma with massive soft tissue involvement [26]. Solitary intraneural neurofibroma and plexiform neurofibroma are considered precursor lesions of malignant PNST.

Histologically, neurofibroma consists of differentiated Schwann cells, perineurial or perineurial-like cells, fibroblasts, mast cells, and residual interspersed myelinated and unmyelinated axons embedded in a myxoid and collagenous extracellular matrix [26]. Specific subtypes may differ from conventional neurofibroma: ancient neurofibroma, cellular neurofibroma, and plexiform neurofibroma [26]. Besides, atypical neurofibromatous neoplasm

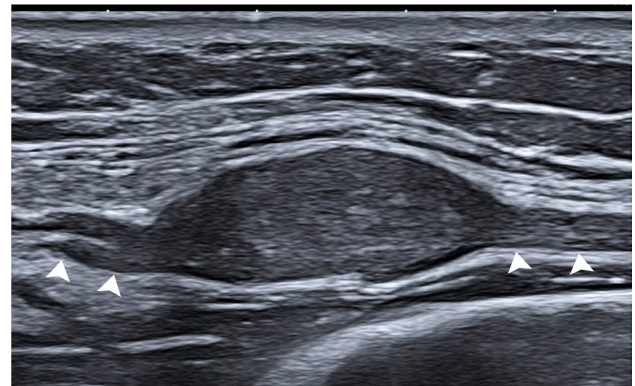


Fig. 6 Neurofibroma. Long-axis US image over the radial nerve in the arm demonstrates a fusiform and hypoechoic mass that exhibits continuity with the nerve at its proximal and distal poles (arrowheads). Note that the lesion appears centrally positioned within the parent nerve

of uncertain biological potential (ANNUBP) is a lesion mainly described in NF1 with increased risk of progression to malignant PNST, that is characterized by at least two of the following worrisome features: hypercellularity, cytological atypia, loss of neurofibroma architecture, and mitotic count (Table 3) [27].

On US, localized intraneural neurofibroma typically appears hypoechoic, fusiform in shape, and demonstrates continuity with the nerve at its proximal and distal poles

(Fig. 6). In contrast with schwannoma, neurofibroma lacks a capsule and tends to infiltrate the involved nerve [7].

On MR imaging, localized neurofibroma shares many morphological features with schwannoma. The tumor typically presents as a fusiform mass that rarely exceeds 5 cm in diameter (Fig. 7). Yet, as opposed to schwannoma, neurofibroma demonstrates a central position within the parent nerve [12]. Neurofibroma frequently exhibits a target sign on T2-weighted images, with central low-signal intensity surrounded by a rim of higher signal intensity, and a predominantly central enhancement pattern after contrast injection [12]. Compared with schwannoma, cystic or hemorrhagic changes are quite uncommon in neurofibroma and should raise suspicion of malignant transformation (Table 2). On DWI, neurofibroma shows higher ADC values ($1.8 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$) than schwannoma ($1.5 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$) with a suggested cutoff at $1.7 \times 10^{-3} \text{ mm}^2/\text{s}$ [25]. On DTI with fiber tractography, because neurofibroma diffusely infiltrates the affected nerve, fiber tracks can appear partially discontinuous, whereas in schwannomas nerve fibers rather run over the tumor capsule (Fig. 7) [25, 28]. On dynamic-enhanced contrast imaging, neurofibroma as well as schwannoma tends to display delayed enhancement [29].

Diffuse neurofibroma with massive soft tissue involvement range in shape from a relatively uniform regional soft tissue enlargement to pendulous bag-like masses (Fig. 8) [26].

Plexiform neurofibroma presents as a multinodular mass, most often affecting a large nerve or plexus, with a bag-of-worms or ropy gross appearance (Fig. 9) [12]. It is highly associated with NF1 [26, 30].

Intraneural perineurioma

Intraneural perineurioma is composed of whorls of perineurial cells surrounding nerve fibers and restricted to the boundaries of a peripheral nerve or plexus [31, 32]. It is a

sporadic condition usually diagnosed during childhood or early adulthood. The location is always focal, with an equal distribution between the upper and lower extremities [33]. Clinically, patients present with focal weakness and atrophy, sometimes associated with sensory symptoms such as numbness or pain of mild severity [33]. This tumor tends to slowly progress to severe functional disability and may spread throughout a nerve, a plexus, or into interconnected nerves over time [34].

Histologically, it presents a characteristic appearance with concentric layers of perineurial cells ensheathing nerve fibers in a pseudo-onion bulb appearance and varying degrees of myelin and axonal loss [31]. By immunohistochemistry, it consistently expresses epithelial membrane antigen (EMA) whereas staining for Schwann cell marker S100 is negative.

On US, the affected nerve presents as a long segment of fusiform enlargement with proximal and distal tapering, and most importantly preservation of the normal nerve fascicular architecture. On MR imaging, the tumor is hypointense to isointense on T1-weighted images, moderately to markedly hyperintense on T2-weighted images, and demonstrates avid enhancement after intravenous contrast injection (Fig. 10). Targeted fascicular biopsy at the site of MR lesion used to be performed as the mainstay of diagnosis [33]. Recently, perineurioma diagnostic criteria have been proposed (age ≤ 40 , no cancer history, unifocal disease, fusiform nerve enlargement, hyperintensity on T2-weighted images, marked and homogeneous contrast enhancement); and their use may obviate the need for tissue when all criteria are present [35].

Malignant perineurioma is very rare. In addition to the cytoarchitectural features described in benign perineurioma, it shows hypercellularity, nuclear atypia, and a high mitotic count [31, 36]. It may metastasize but appears to behave less aggressively than conventional malignant PNST.

Fig. 7 Neurofibroma. Coronal fat-suppressed T2-weighted maximum intensity projection (MIP) image (a) demonstrates a fusiform mass of the C5 root of the right brachial plexus (thick arrow). On tractography (b), because neurofibroma diffusely infiltrates the affected nerve, fiber tracks appear to be partially discontinuous (thick arrow)

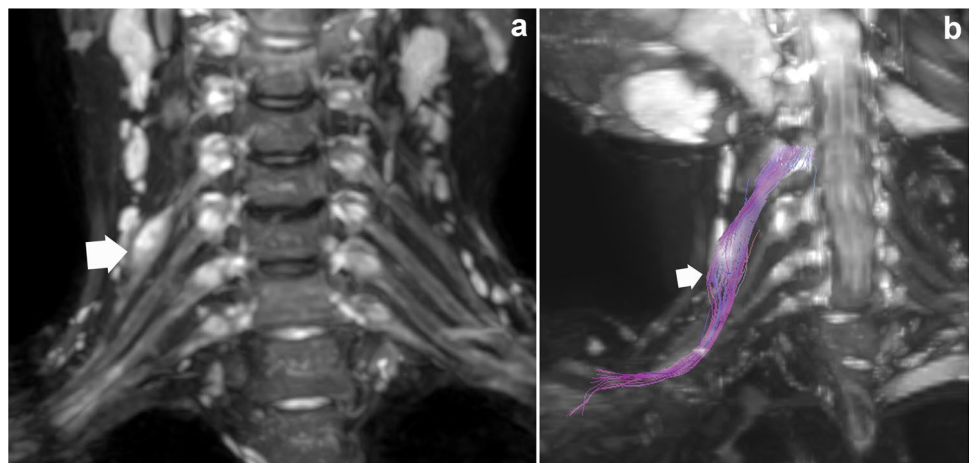




Fig. 8 Diffuse neurofibroma. Coronal T1-weighted MR image demonstrating a massive diffuse soft tissue tumor (thick arrows) involving the skin and subcutaneous tissue of the right lower limb and vulva, with pendulous bag-like masses

Hybrid nerve sheath tumor

Hybrid nerve sheath tumor is a very rare benign PNST that exhibits combined features of more than one conventional type (schwannoma, neurofibroma, perineurioma) [37]. Clinical presentation appears similar to that of conventional PNST with either painless subcutaneous or skin masses, or, when peripheral nerves or spinal nerves are involved, tumors can be associated with pain or neurological deficit. Histologically, hybrid nerve sheath tumor is generally well circumscribed and exhibits intermingled



Fig. 9 Plexiform neurofibroma. Coronal STIR MR image in a patient with neurofibromatosis type 1 showing a multinodular tumor enlarging and replacing the right sciatic nerve (thick arrows), imparting a bag-of-worms appearance

features of two types of benign PNST [37]. The two components are highlighted by immunohistochemistry [37].

Hybrid schwannoma/perineurioma is the most common subtype and occurs sporadically (Fig. 11). Hybrid schwannoma/neurofibroma is strongly associated with NF1, NF2, and schwannomatosis. Hybrid neurofibroma/perineurioma is quite exceptional and has been reported in association with NF1 [38].

Neuromuscular choristoma

Neuromuscular choristoma, or benign triton tumor, is an expansile intraneural mass characterized by the intimate interposition of mature skeletal muscle and nerve fibers within the endoneurium [39]. It is considered an extremely rare condition. The tumor may involve large nerves or plexuses, most commonly the sciatic nerve and brachial plexus. Clinically,

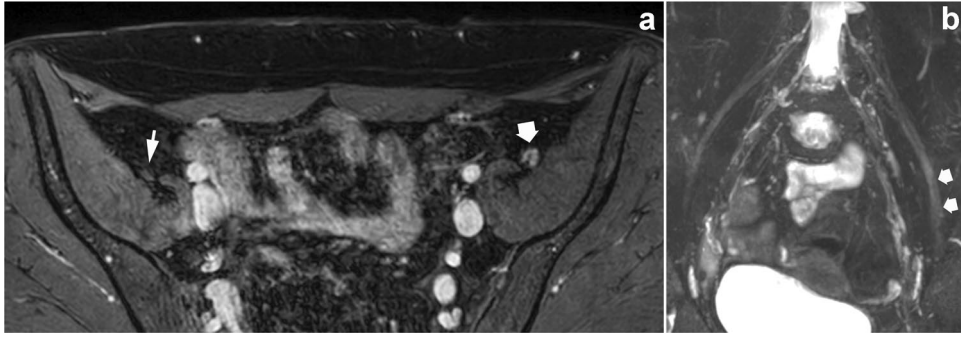
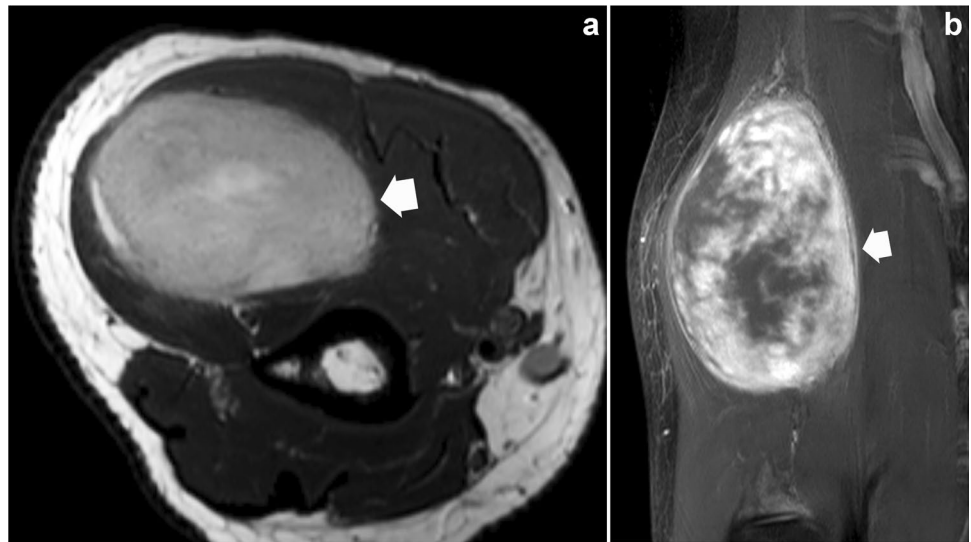


Fig. 10 Intraneural perineurioma. Axial post-contrast fat-suppressed T1-weighted MR image (a) showing avid enhancement and hypertrophy of the left femoral nerve (thick arrow) in comparison with the right femoral nerve (thin arrow). Coronal fat-suppressed T2-weighted

maximum intensity projection (MIP) image (b) demonstrates fusiform enlargement of the left femoral nerve (thick arrows) with proximal and distal tapering

Fig. 11 Hybrid schwannoma/perineurioma. Axial T2-weighted (a) MR image showing a well-defined mass of high-signal intensity in the anterior compartment of the right arm (thick arrow). Coronal post-contrast fat-suppressed T1-weighted MR image (b) displays heterogeneous peripheric enhancement (thick arrow)



patients present with progressive pain, neurological deficit, and sometimes atrophy of the affected limb.

Superimposed desmoid fibromatosis is present in as many as 80% of cases [40]. Conversely, an occult neuromuscular choristoma precursor may be present in as many as 5% of sporadic limb-associated desmoids suggesting that the neuromuscular choristoma–fibromatosis association might be underdiagnosed [41]. Because in this entity there is frequent postsurgical development of desmoid fibromatosis, a no-touch approach is advocated for patients with typical clinical and imaging features [39].

On MR imaging, neuromuscular choristoma demonstrates similar signal intensities on T1-weighted and T2-weighted images to those of adjacent skeletal muscle [39]. When a desmoid fibromatosis component is present, it features hypointense T1 and T2 signals compared with skeletal muscle and shows marked enhancement after contrast injection.

Malignant peripheral nerve sheath tumor

Malignant PNST (MPNST) accounts for approximately 3–5% of soft tissue sarcomas [4, 42]. It can be encountered in middle-aged adults, often in the setting of NF1 or following radiation therapy. In contrast with benign PNST, MPNST is usually larger than 5 cm, with a rapid growth pattern and worsening of neurological symptoms (Table 4). This tumor is a high-grade sarcoma with a poor prognosis. Truncal location, size > 5 cm, high-grade morphology, local recurrence, and association with NF1 are adverse prognosis factors [43].

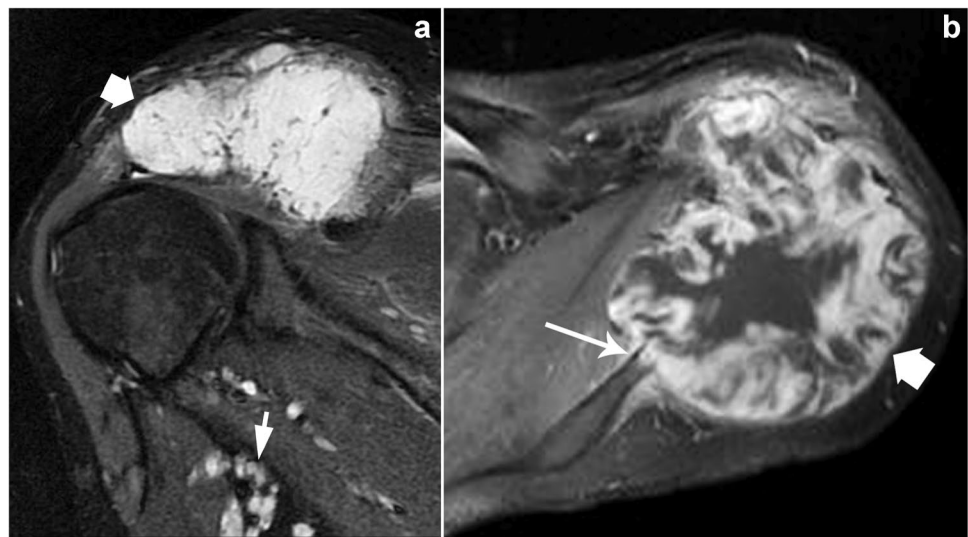
In NF1 patients, the lifetime risk for MPNST is estimated at 9–13% [44]. Patients are often younger at the time of diagnosis than patients with sporadic tumors. Thus, in the setting of NF1, MPNST must be suspected in case of a distinct growing mass on MR imaging or increased activity on PET (Fig. 12) [45].

Histologically, it presents as a malignant spindle cell tumor usually arising from a peripheral nerve or from a

Table 4 Clinical, conventional, and advanced MR imaging features of benign and malignant PNST

	Benign PNST	Malignant PNST
Clinical symptoms	Rare	Frequent
Weakness/sensory deficit	Rare	Common
Growth pattern	Slow	Rapid
Size	< 5 cm	> 5 cm
Signal	Homogeneous, target sign	Heterogeneous, no target sign
Necrosis/cystic change	Uncommon	Common
Margins	Well-defined	Well- or ill-defined
Perilesional edema	Absent	Common
Enhancement pattern	Homogeneous or targetoid	Heterogeneous, not targetoid
DTI	Minimum ADC values > $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$	Minimum ADC values < $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$
Tractography	Normal or partially disrupted nerve tracts	Partially or completely disrupted nerve tracts

Fig.12 Malignant PNST. Coronal STIR MR image (a) in a patient with neurofibromatosis type 1 showing a multilobulated mass of high-signal intensity (thick arrow) of the right acromion. Of note, in the axillary fossa, the brachial plexus cords (thin arrow) appear thickened and hyperintense in keeping with NF 1. Axial post-contrast fat-suppressed T1-weighted MR image (b) demonstrates heterogeneous enhancement with central necrosis (thick arrow) and osteolysis of the adjacent spine of the scapula (thin arrow)



preexisting benign PNST [42]. Immunohistochemically, MPNST exhibits focal or patchy staining for S100 or SOX10, and/or loss of H3K27me3 expression [42].

On MR imaging, MPNST often exhibits ill-defined margins with adjacent soft tissue invasion and perilesional edema (Fig. 13) [42]. The tumor demonstrates a heterogeneous signal with areas of hemorrhage and necrosis, and displays a heterogeneous peripheral enhancement pattern after contrast injection (Fig. 14). When the tumor does not involve a peripheral nerve, the diagnosis only relies on the histological features because there are no specific imaging findings that can distinguish MPNST from other soft tissue sarcomas [42].

Malignant melanotic nerve sheath tumor

Malignant melanotic nerve sheath tumor is a rare peripheral nerve sheath tumor composed uniformly of Schwann cells showing melanocytic differentiation, usually arising from the spinal or

autonomic nerves near the midline [46]. Presenting symptoms include pain, sensory abnormalities, and mass effect. This entity frequently shows aggressive clinical behavior with a risk of local recurrence and metastases [47]. On MR imaging, the tumor demonstrates high-signal intensity on T1-weighted images and low-signal intensity on T2-weighted images reflecting the presence of melanin pigment within the tumor [46].

Malignant melanotic nerve sheath tumor may sometimes be associated with Carney complex, an autosomal dominant multiple neoplasia syndrome. In patients with Carney complex, multiple and multicentric tumors may be observed, especially in the gastrointestinal tract, paraspinal sympathetic chain, and chest wall [46].

Other neoplasms of peripheral nerves

Granular cell tumor is a tumor showing neuroectodermal differentiation and composed of epithelioid to polygonal cells with abundant granular eosinophilic cytoplasm [48].

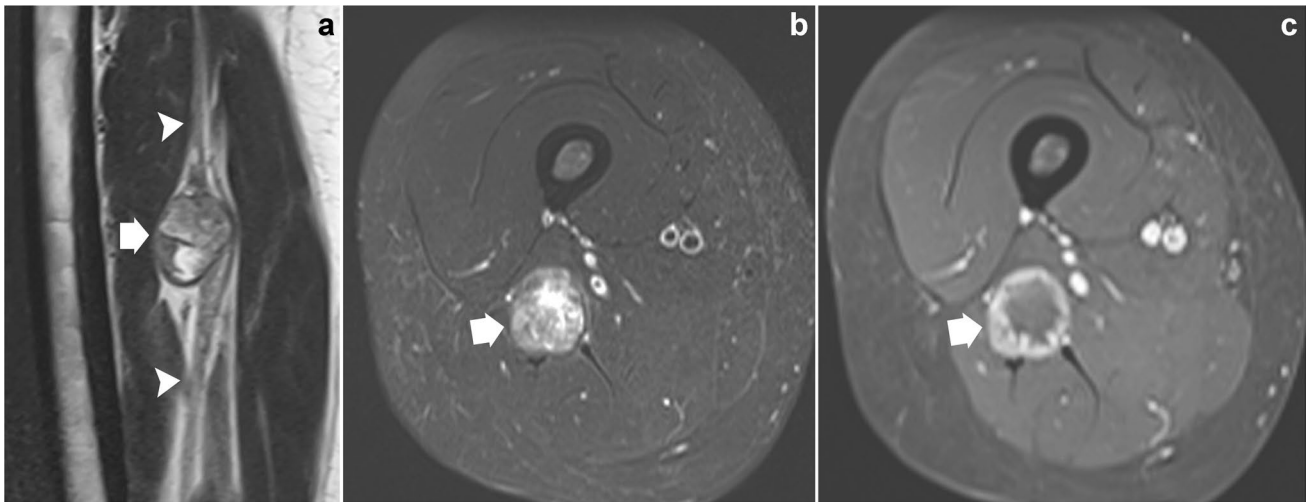
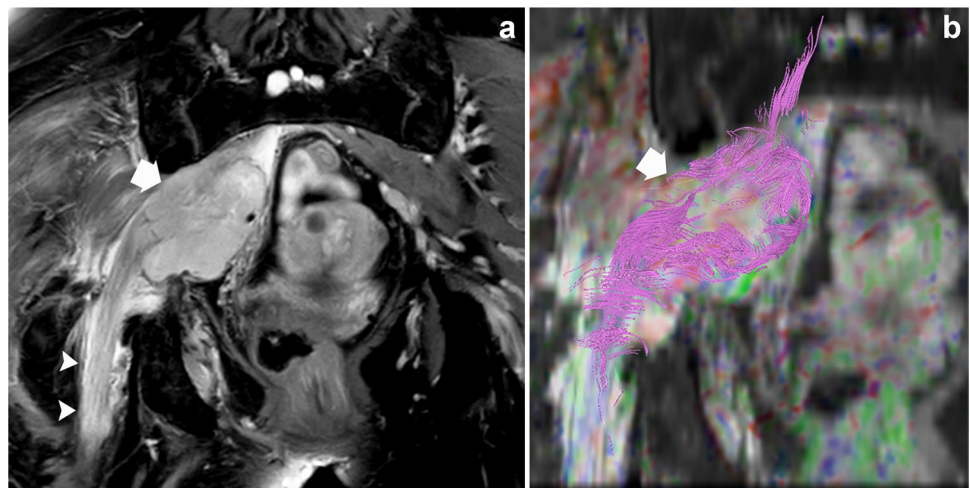


Fig. 13 Malignant PNST. Sagittal T2-weighted (a) and axial STIR (b) MR images demonstrating a mass (thick arrow) involving the right sciatic nerve (arrowheads) that exhibits heterogeneous signal

with no target sign. Axial post-contrast fat-suppressed T1-weighted MR image (c) shows heterogeneous enhancement with central necrosis (thick arrow)

Fig. 14 Malignant PNST. Coronal fat-suppressed T2-weighted MR image (a) shows a large and ill-defined mass (thick arrow) involving the right sacral plexus and sciatic nerve (arrowheads). On tractography (b), fiber tracts appear completely disrupted (thick arrow)



It can affect the skin, tongue, breast, and less commonly gastrointestinal and respiratory tracts. In the vast majority of cases, granular cell tumor is benign.

Nerve sheath myxoma is a rare and benign PNST that typically arises in the skin or subcutis and often presents a multinodular growth pattern [49].

Desmoid fibromatosis is a locally aggressive but non-metastasizing deep-seated neoplasm with infiltrative growth and propensity for local recurrence. Desmoid fibromatosis may progress along the fascial planes and long axis of the peripheral nerve or plexus (Fig. 15). On MR imaging, the tumor typically presents as an irregular and infiltrative mass that demonstrates mixed hypointense and hyperintense signals on T2-weighted images, and avid enhancement following contrast injection [50].

Tenosynovial giant cell tumor is a benign tumor that most often arises from the synovium of joints, bursae, and tendon sheaths, and shows synovial differentiation with variable proportions of small histiocytic cells, large amphophilic cells, foam cells, multinucleated cells, and hemosiderin. This tumor can rarely be adherent to major peripheral nerves and cause extrinsic nerve compression [51]. MR imaging is helpful for the diagnosis of this entity because of its characteristic low-signal intensity on T2-weighted images with a blooming effect on gradient-echo sequences reflecting the paramagnetic effect of hemosiderin within the tumor, and, on DWI, low ADC value (Fig. 16) [51, 52].

Synovial sarcoma is a malignant soft tissue tumor of uncertain differentiation characterized by a specific *SS18-SSX1/2/4* fusion gene. Rarely, synovial sarcoma can arise

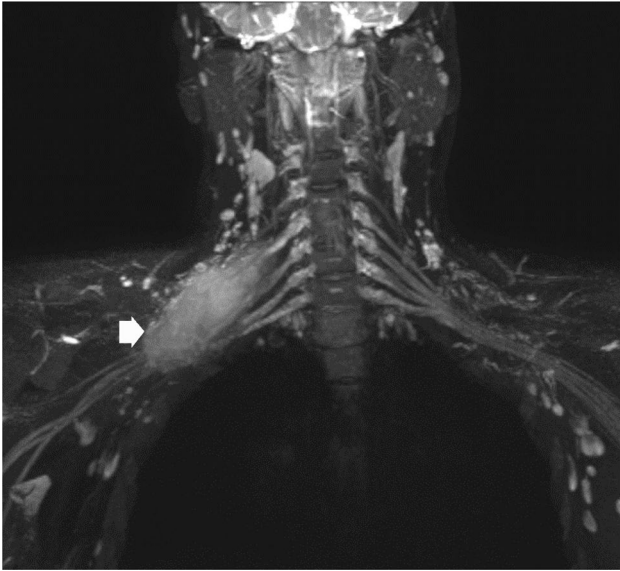


Fig. 15 Desmoid tumor. Coronal fat-suppressed T2-weighted maximum intensity projection (MIP) MR image showing an irregular and infiltrative mass (thick arrow) involving the superior and middle trunks of the right brachial plexus which extends laterally along the divisions of the brachial plexus

within the peripheral nerves [53]. This tumor can pose diagnostic difficulties because it may demonstrate imaging features similar to benign PNST [54]. Despite being malignant, it usually presents as a small, slow-growing, often painful soft tissue mass. On MR imaging, synovial sarcoma of the peripheral nerve presents as a well-defined tumor with a clear connection to the parent nerve, and exhibits a hypointense signal on T1-weighted images, a heterogeneous intermediate-to-hyperintense signal on fat-suppressed T2-weighted images, and an early arterial phase post-contrast enhancement (Fig. 17). The lack of target sign, irregular margins, peritumoral edema, and, on DWI, low ADC value may be helpful in the distinction of synovial sarcoma [55]. Histologically, the main differential diagnosis is MPNST which can show morphologic and immunophenotypical overlap with synovial sarcoma [54].

Neurolymphoma refers to nerve infiltration by neurotropic neoplastic lymphocytes, related to non-Hodgkin's lymphoma in 90% and to acute leukemia (chloroma) in 10% of cases. It may show various clinical presentations that include painful peripheral neuropathy or radiculopathy, cranial neuropathy, painless polyneuropathy, or

Fig. 16 Tenosynovial giant cell tumor. Coronal in and water-only T2-weighted DIXON MR images showing a soft tissue mass (thick arrow) of the right buttock involving the sciatic nerve that exhibits characteristic low-signal intensity

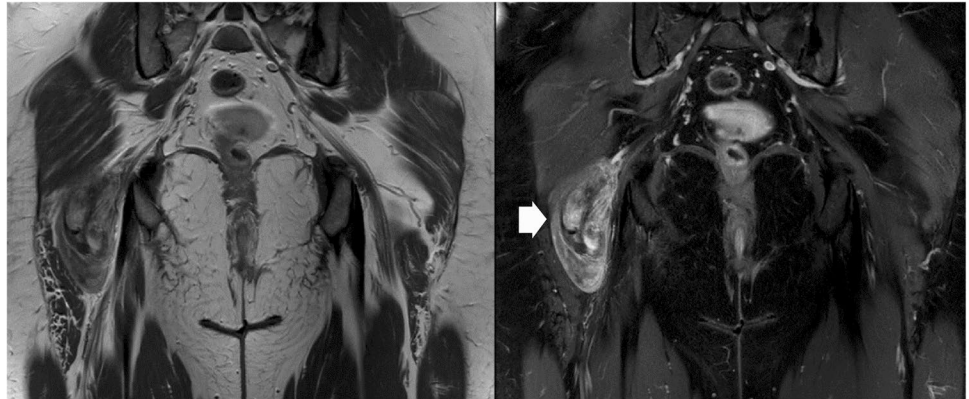


Fig. 17 Synovial sarcoma. Sagittal T1-weighted (a) and corresponding fat-suppressed T2-weighted (b) MR images demonstrating a relatively well-defined tumor (thick arrow) with a clear connection to the sciatic nerve (arrowhead) that exhibits inhomogeneous signal with fluid–fluid level and triple signal intensity



mononeuropathy multiplex [50]. Primary neurolymphomatosis is an exceptional manifestation of high-grade B cell lymphoma characterized by the involvement of a peripheral nerve or plexus in isolation and without systemic manifestations [56]. The lesion may present as uniform thickening of a long segment of a major nerve and its branches, with a predilection for the sciatic nerve. Yet, neurolymphoma is most commonly related to enlarged lymph nodes that compress and infiltrate the peripheral nerve, or plexus. MR imaging typically demonstrates a diffuse enlargement of the peripheral nerve or plexus, with often multifocal nodularity, in a patient with a known systemic lymphoma or in an immune-compromised individual (Fig. 18). On T2-weighted images, there can be internal interspersed hypointensities [50]. After contrast injection, there is marked homogeneous or more frequently heterogeneous enhancement. On DTI, neurolymphoma shows near-normal to partially disrupted tracts, and, on DWI, low ADC value [28].

Nerve involvement in *carcinoma metastases* can occur by direct extension or spread of disease from adjacent lymph nodes rather than by intraneural development. The most common site for neural involvement by metastatic disease is the brachial plexus with breast and lung carcinomas [57]. Findings that suggest a metastasis rather than a primary nerve neoplasm are, in addition to the history of cancer, the presence of multiple lesions, the infiltrative tumor margins, and the enlargement of adjacent lymph nodes [6].



Fig. 18 Non-Hodgkin lymphoma. Coronal T2-weighted MR image showing a large deep soft tissue mass (thick arrow) in the anterior compartment of the left thigh that infiltrates the femoral nerve (arrowhead) superiorly, immediately lateral to the femoral artery

Non-neoplastic conditions mimicking peripheral nerve sheath tumor

Traumatic neuroma is a non-neoplastic focal nerve enlargement which results from severe nerve damage such as Sunderland grades III, IV, and V nerve injuries, or from repeated microtrauma. At histopathology, traumatic neuroma includes nonencapsulated tangled masses of axons, Schwann cells, endoneurial cells, and perineurial cells in a dense collagenous stroma with surrounding fibroblasts [58, 59]. Disorganization of the neurogenic tissue with multidirectional cell proliferation in an attempt to repair the nerve injury allows traumatic neuroma to be differentiated from neurofibroma [12].

Patients present with numbness and sensory loss in the relevant territory of innervation and often neuropathic pain with a trigger point at the level of the neuroma. On US, the lesion may present either as spindle neuroma with focal, hypoechoic, homogeneous, lenticular nerve swelling without disruption of the nerve fibers, or as terminal neuroma with stump enlargement of the proximal end of a transected nerve (Fig. 19). Scar encasement characterized by fibrous tissue surrounding the nerve represents a third type of injury that can be either isolated or associated with the two previous subtypes [59].

Ganglion cyst can infrequently occur within the epineurium of peripheral nerves, involving in particular the peroneal or tibial nerves about the knee [60]. Cyst formation originates in the proximal tibiofibular joint and propagates toward the nerve through its articular branch. Histologically, nerve sheath ganglion demonstrates myxoid change surrounded by a fibrous lining, and typically tracks along the epineurium resulting in displacement of the adjacent nerve

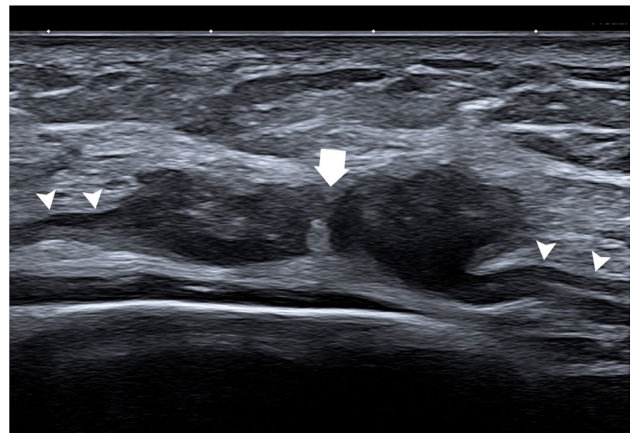


Fig. 19 Traumatic neuroma. Long-axis US image over the radial nerve in the arm exhibiting nerve swelling (arrowheads), with disruption of the nerve fibers (thick arrow) and hypoechoic enlargement of the proximal and distal ends of the transected nerve

itself. Patients may present with neurologic symptoms from nerve compression and sometimes a palpable soft tissue mass. At US and MR imaging, the lesion appears as a purely cystic formation that may contain thin internal septations [7]. Surgical resection is proposed in symptomatic cases with cautious identification of the lesion neck to prevent recurrence.

Lipomatosis of nerve is a rare tumor-like hamartomatous condition characterized by the overgrowth of mature fibroadipose tissue within the epineurium, surrounding and separating nerve fascicles [61]. The tumor affects more frequently the upper extremity than the lower extremity, with the most frequently peripheral nerves affected being the median nerve for approximately two-thirds of cases, followed by the plantar and ulnar nerves [62]. Patients classically present in the first decade of life, with slowly progressive sensory loss and paresthesias, sometimes associated with pain and muscle weakness, related to a compression neuropathy especially at the carpal tunnel. Overgrowth in the nerve distribution territory has been reported in more than 60% of cases, with digital enlargement referred to as macrodystrophia lipomatosa [63]. On MR imaging, this lesion demonstrates a pathognomonic coaxial cable-like appearance in the horizontal plane and a spaghetti-like appearance in the longitudinal axis, with serpentine thickened nerve fascicles surrounded by fat or fibrofatty tissue (Fig. 20).

Intraneural venous malformation is exceptional, and has been reported in the median nerve either presenting as a painless mass or causing median nerve compression [64].

Charcot-Marie-Tooth (CMT) disease is a genetically transmitted group of peripheral neuropathies with an estimated prevalence of 1 in 2500. Because over 100 different genes are known to be responsible for various forms of CMT, and because approximately one-third of patients do not have any family history, making a diagnosis of CMT may be difficult. On MR imaging, CMT can appear as a mass-like symmetrical enlargement of the peripheral nerves that can mimic neurocutaneous syndromes [8, 50]. Pseudomasses resulting from excessive demyelination and remyelination can in particular be observed in the brachial and/or lumbosacral plexus (Fig. 21). On contrast images, there is minimal to no enhancement.

Peripheral nerve amyloidosis can result in fusiform neural swelling with the maintenance of the fascicular architecture, variable enhancement, and muscular denervation changes. Amyloid neuropathy most commonly presents as a length-dependent sensorimotor polyneuropathy with multifocal involvement of lumbosacral plexus segments or sciatic nerves. In contrast, in its focal presentation, peripheral nerve amyloidoma is characterized by a mass-like enhancing neural enlargement, and may mimic the appearance of both benign and malignant peripheral nerve processes [65].

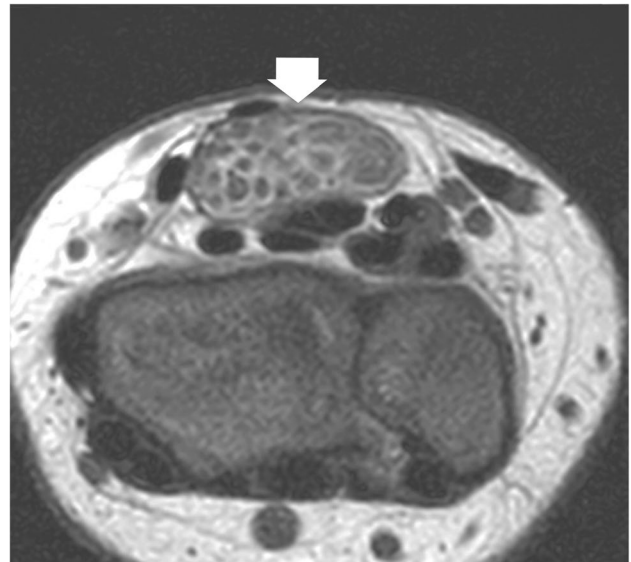


Fig. 20 Lipomatosis of nerve. Axial T1-weighted MR image of the right wrist showing the pathognomonic coaxial cable-like appearance with thickened nerve fascicles surrounded by fat or fibrofatty tissue (thick arrow)



Fig. 21 Charcot-Marie-Tooth disease. Coronal fat-suppressed T2-weighted MR image displaying mass-like symmetrical enlargement of the brachial plexus (thick arrows) mimicking neurocutaneous syndromes

Conclusion

High-resolution US and MR imaging are the modalities of choice for diagnosing neurogenic tumors. The first step is to establish a nerve–tumor relationship and therefore exclude other diagnoses. Then, with a combination of clinical features, anatomical location, and imaging appearances, it is usually possible to characterize neurogenic tumors confidently. Yet, despite recent advances in US and MR imaging, the preoperative differentiation between schwannoma and localized neurofibroma may remain difficult in some cases because these two benign PNSTs share many imaging features. Another diagnostic challenge consists in the differentiation between large benign PNST and MPNST. In this setting, a carefully planned surgical excision biopsy remains advocated.

Declarations

Conflict of interest The authors declare no competing interests.

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