The case:

A 45-year-old woman with a history of neurofibromatosis presented with pain and numbness in her left foot for the past 3 months. She noted that a mass had been present in the medial aspect of left ankle for several years, but only in the past months had it caused paresthesia over the plantar foot and tarsal tunnel. Physical examination confirmed a tender mass in the medial aspect of her left ankle, and magnetic resonance images (A-C) were obtained.

Figure: T1-weighted sagittal (A) and axial (B) and T2-weighted sagittal fast spin-echo fat-suppressed (C) magnetic resonance images of the left ankle.

Your diagnosis?

For answer see page 154
Diagnosis:

Neurofibroma Causing Tarsal Tunnel Syndrome

Anika L. Mirick, BA; Gerald B. Bornstein, DPM; Laura W. Bancroft, MD

A 45-year-old woman with a history of neurofibromatosis presented with a palpable mass in her tarsal tunnel and a 3-month history of left foot pain and numbness. Magnetic resonance imaging (MRI) confirmed a 4.5 × 1.7 × 1.6-cm well-circumscribed, ovoid mass within the tarsal tunnel, consistent with a neurofibroma (Figure 1). A presumptive diagnosis of neurofibroma causing tarsal tunnel syndrome was made based on imaging and physical examination findings, and surgical resection confirmed the diagnosis.

Neurofibromatosis

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is a neurocutaneous syndrome characterized by the presence of multiple café-au-lait spots, axillary and inguinal freckling, cutaneous neurofibromas, Lisch nodules, and plexiform neurofibroma. Orthopedic manifestations include scoliosis, dysplasia of long bones (primarily the tibia) (Figure 1) leading to pathologic fractures and pseudoarthrosis, focal dysplasia (primarily of the ulna, scapula, and vertebra), short stature, osteopenia, and osteoporosis.¹

Neurofibromatosis type 1 has an incidence of 1 in 3000 individuals, making it one of the most common hereditary diseases.² It is inherited in an autosomal dominant pattern, although de novo mutations may be responsible for up to 50% of cases.² The syndrome results from the biallelic deletion of the NF1 tumor suppressor gene that encodes neurofibromin, a GTPase-activating protein, which hydrolyzes guanosine and triphosphate, that normally downregulates the Ras/MAPK signaling cascade for cellular growth.² Neurofibromatosis type 1 is associated with several neoplasms,
Nerve Sheath Tumors

Peripheral nerve sheath tumors associated with NF1 are classified as benign (eg, neurofibroma, plexiform neurofibroma, neurilemmoma, or schwannoma) or malignant. Neurofibroma and neurilemmoma arise from nonmyelinating Schwann cells in the peripheral nervous system. Neurilemmoma arises solely from these cells, whereas neurofibroma incorporates collagen and myxoid material from fibroblasts.

Neurofibroma is classified into cutaneous, subcutaneous, and plexiform subtypes. Plexiform neurofibroma can involve multiple fascicles within a single nerve, multiple nerves, or entire nerve plexuses. Plexiform neurofibroma is pathognomonic for NF1 and is the only type of neurofibroma with malignant potential. Approximately 10% of plexiform neurofibromas undergo malignant transformation into malignant PNSTs due to the loss of CDKN2A and TP53, which will occur in 4.6% to 13% of patients with NF1 and are found in isolation, whereas neurofibromas are often multiple.\(^5\,^6\)

Plexiform neurofibroma is a congenital lesion that presents in early infancy.\(^7\) As with neurofibromas, the highest growth rate of plexiform neurofibroma occurs during childhood, puberty, and pregnancy. Lesions often present as palpable, cord-like masses (called a bag of worms) accompanied by soft tissue thickening and skin hyperpigmentation. Plexiform neurofibroma can grow to extreme sizes, causing whole limb disfigurement, a condition known as elephantiasis neurofibromatosa.\(^3\) However, plexiform neurofibroma most commonly presents with painless peripheral edema, limited range of motion of a limb, and tenderness to palpation. Plexiform neurofibroma develops in 50% of patients with NF1, and malignant degeneration usually occurs between age 20 and 30 years.\(^1\)

Clinical symptoms of malignant transformation include rapid expansion or increased firmness of a known neurofibroma, persistent pain or rest pain, and new neurological deficits, particularly severe motor weakness.\(^7\,^8\) Malignant PNSTs have a poor prognosis, with a 15% to 30% five-year survival rate.\(^9\) Common sites of metastases include the lungs, bones, and pleura, whereas lymph nodes are not commonly involved.\(^7\)

**IMAGING Neurofibroma and Neurilemmoma**

Neurofibroma presents as a small, well-circumscribed, hypodense mass on noncontrast computed tomography (CT) and demonstrates slight homogeneous or heterogeneous enhancement (20 to 25 Hounsfield units nonenhanced, 30 to 50 Hounsfield units enhanced).\(^2\) Characteristic MRI findings include low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and strong enhancement (Figure 2).\(^10\) Neurofibroma is typically heterogeneously hypointense on T2-weighted MRI, with low signal areas corresponding with fibrous and collagenous regions and high signal areas corresponding to myxomatous stroma and cystic degeneration (Figure 2).\(^2\) Benign features of neurofibroma are best seen with MRI.

The fat-split sign on T1-weighted MRI is a peripheral brim of fat surrounding the le-
tion, representing the maintenance of the normal fat around the neurovascular bundle. The target sign is a hypointense central area on T2-weighted MRI that corresponds with fibrosis, with a more hyperintense myxomatous stroma in the margins of the tumor (Figure 2). The target sign has been demonstrated in 58% of neurofibromas and 15% of neurilemmomas in a study by Jee et al. Neurilemmoma and neurofibroma are difficult to differentiate on MRI because both can have a fusiform shape and can exhibit the fat-split and target signs. However, neurofibroma is centrally positioned relative to the nerve, whereas neurilemmoma is more eccentric (Figure 3). Neurilemmoma also tends to be more heterogeneous due to relative increases in the number of cystic cavitations, calcifications, and areas of central necrosis.

Plexiform Neurofibroma

Plexiform neurofibroma is similar to neurofibroma but has a larger, more complex ring-like configuration on MRI. It is typically a large, multiseptated low-attenuated mass seen in a medium to large nerve distribution on CT. Magnetic resonance imaging is best for showing the ring-like structure of this tumor (Figure 4). Often, the target sign will be present in multiple locations within the mass (Figure 4).

Malignant Peripheral Nerve Sheath Tumors

Magnetic resonance imaging can be useful in monitoring the size and boundaries of PNSTs, but it cannot reliably detect malignancy (Figure 5). Although both benign and malignant PNSTs can have irregular borders, soft tissue and bony destruction, features such as size (larger than 5 cm²), infiltrative borders, areas of central necrosis and calcifications, intratumoral lobulations, heterogeneous enhancement, and surrounding edema are more common with malignancy. Wasa et al. found that a large mass (5-9 cm) with peripheral enhancement, surrounding edema, T1-weighted heterogeneity, and areas of cystic degeneration on MRI was predictive of malignancy with a sensitivity of 61% and a specificity of 90%. The authors recommended that masses with 2 or more of these features should undergo a biopsy. Nuclear medicine studies, such as 67-gallium-citrate scintigraphy and 18-fluoro-deoxyglucose (FDG)-PET, are considered the most sensitive indicators of malignant degeneration. Although only malignant tumors uptake 67-gallium citrate, a small portion of malignant PNSTs will be positive for this test, limiting its clinical applicability. However, FDG-PET has the ability to detect malignant PNSTs with a sensitivity of 98% and specificity of 95%. Any lesion with a maximum standardized uptake value more than 7 is highly suspicious for malignancy, and some believe that lesions with a maximum standardized uptake value greater than 3.5 warrant biopsy.

A limitation of FDG-PET is the poor uptake of isotope by low-grade malignant PNSTs, making it difficult to differentiate these tumors from benign plexiform neurofibromas. For high-grade lesions, FDG-PET is able to detect malignancy with a sensitivity approaching 100% in 1 study, although a recent case reported a false-negative FDG-PET in a woman with NF1 and high-grade metastatic malignant PNST.

In addition, FDG-PET/CT is useful in directing biopsy toward the highest-grade
part of a heterogenous lesion. Together, MRI and FDG-PET are the most sensitive and specific imaging modalities to monitor malignant transformation, although histological biopsy is required for definitive diagnosis.

**TREATMENT**

Symptomatic neurofibroma and neurilemoma are treated with surgical excision. Neurilemoma is removed by enucleation of the tumor; if the capsule is fibrosed to the parent nerve, it can be left. Neurofibroma is more difficult to remove because it does not have a capsule and is adherent to the underlying nerve. If the tumor is small, it is removed en bloc.

Plexiform neurofibroma requires a more careful dissection, and intraoperative neurophysiological monitoring is often used to determine the functionality of the involved nerve. Only nerve fascicles that are directly entering, exiting, or nonfunctional are removed. Nerves with motor function greater than 1 mA are not removed, even if that necessitates leaving residual tumor.

Due to its infiltrative nature, plexiform neurofibroma has a high rate of local recurrence. Radiofrequency ablation performed for the treatment of a craniofacial plexiform neurofibroma in 5 children showed partial diminution or stabilization of lesions. However, radiation therapy is contraindicated because it can result in malignant degeneration.

Malignant PNSTs require wide surgical resection, adjuvant or neoadjuvant radiation, and chemotherapy. Amputation of the limb may be required if the tumor has developed its own nervous supply or limb salvage is not possible. Limb salvage may be possible with wide local resection and postoperative radiation therapy and is only appropriate when no evidence of metastases exists.

Chemotherapy consists of ifosfamide, doxorubicin, and cisplatin and is reserved for large (larger than 5 cm), high-grade tumors with distant metastases. Palliative care for unresectable lesions includes a combination of chemotherapy, radiation, and surgical debulking for painful or obstructive symptoms. Complications from surgery include loss of limb function, sensory and motor deficit, and neurogenic pain syndrome. Given the variable and wide presentation of complex problems associated with NF1, monitoring of these individuals should be performed by a multidisciplinary team.

**REFERENCES**