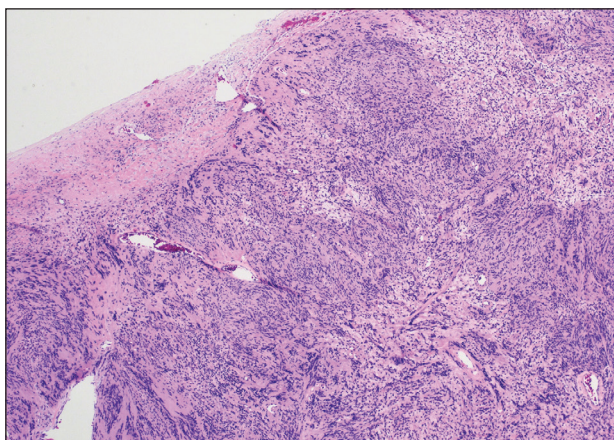


Soft Nodule on the Forearm

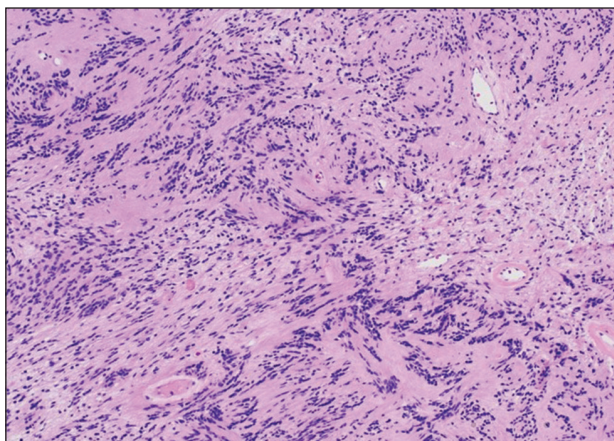
Syeda F. Absar, MD, MPH; Tammie C. Ferringer, MD

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H&E, original magnification ×40.



H&E, original magnification ×100.

A 54-year-old woman presented with an enlarging mass on the right volar forearm. Physical examination revealed a 1-cm, soft, mobile, subcutaneous nodule. Excision revealed tan-pink, indurated, fibrous, nodular tissue.

THE BEST DIAGNOSIS IS:

- a. angioleiomyoma
- b. neurofibroma
- c. nodular fasciitis
- d. schwannoma
- e. solitary circumscribed neuroma

PLEASE TURN TO **PAGE 187** FOR THE DIAGNOSIS

From the Department of Pathology, Geisinger Medical Center, Danville, Pennsylvania. Dr. Ferringer also is from the Department of Dermatology. The authors report no conflict of interest.

Correspondence: Syeda F. Absar, MD, MPH, Department of Pathology, Geisinger Medical Center, 100 N Academy Ave, Mailstop 19-20, Danville, PA 17822 (sabsar1@geisinger.edu).

doi:10.12788/cutis.0357

THE DIAGNOSIS: Schwannoma

Schwannoma, also known as neurilemmoma, is a benign encapsulated neoplasm of the peripheral nerve sheath that presents as a subcutaneous nodule.¹ It also may present in the retroperitoneum, mediastinum, and viscera (eg, gastrointestinal tract, bone, upper respiratory tract, lymph nodes). It may occur as multiple lesions when associated with certain syndromes. It usually is an asymptomatic indolent tumor with neurologic symptoms, such as pain and tenderness, in the lesions that are deeper, larger, or closer in proximity to nearby structures.^{2,3}

Histologically, a schwannoma is encapsulated by the perineurium of the nerve bundle from which it originates (quiz image [top]). The tumor consists of hypercellular (Antoni type A) and hypocellular (Antoni type B) areas. Antoni type A areas consist of tightly packed, spindle-shaped cells with elongated wavy nuclei and indistinct cytoplasmic borders. These nuclei tend to align into parallel rows with intervening anuclear zones forming Verocay bodies (quiz image [bottom]).⁴ Verocay bodies are not seen in all schwannomas, and similar formations may be seen in other tumors as well. Solitary circumscribed neuromas also have Verocay bodies, whereas dermatofibromas and leiomyomas have Verocay-like bodies. Antoni type B areas have scattered spindled or ovoid cells in an edematous or myxoid matrix interspersed with inflammatory cells such as lymphocytes and histiocytes. Vessels with thick hyalinized walls are a helpful feature in diagnosis.² Schwann cells of a schwannoma stain diffusely positive with S-100 protein. The capsule stains positively with epithelial membrane antigen due to the presence of perineurial cells.²

The morphologic variants of this entity include conventional (common, solitary), cellular, plexiform, ancient, melanotic, epithelioid, pseudoglandular, neuroblastomalike, and microcystic/reticular schwannomas. There are additional variants that are associated with genetic syndromes, such as multiple cutaneous plexiform schwannomas linked with neurofibromatosis type 2, psammomatous melanotic schwannoma presenting in Carney complex, schwannomatosis, and segmental schwannomatosis (a distinct form of neurofibromatosis characterized by multiple schwannomas localized to one limb). Either presentation may have alteration or deletion of the neurofibromatosis type 2 gene, *NF2*, on chromosome 22.^{2,5}

Nodular fasciitis is a benign tumor of fibroblasts and myofibroblasts that usually arises in the subcutaneous tissues. It most commonly occurs in the upper extremities, trunk, head, and neck. It presents as a single, often painful, rapidly growing, subcutaneous nodule. Histologically, lesions mostly are well circumscribed yet unencapsulated, in contrast to schwannomas. They may be hypocellular or

hypercellular and are composed of uniform spindle cells with a feathery or fascicular (tissue culture–like) appearance in a loose, myxoid to collagenous stroma. There may be foci of hemorrhage and conspicuous mitoses but not atypical figures (Figure 1). Immunohistochemically, the cells stain positively for smooth muscle actin and negatively for S-100 protein, which sets it apart from a schwannoma. Most cases contain fusion genes, with myosin heavy chain 9 ubiquitin-specific peptidase 6, *MYH9-USP6*, being the most common fusion product.⁶

Solitary circumscribed neuroma (palisaded encapsulated neuroma) is a benign, usually solitary dermal lesion. It most commonly occurs in middle-aged to elderly adults as a small (<1 cm), firm, flesh-colored to pink papule on the face (ie, cheeks, nose, nasolabial folds) and less commonly in the oral and acral regions and on the eyelids and penis. The lesion usually is unilobular; however, other growth patterns such as plexiform, multilobular, and fungating variants have been identified. Histologically, it is a well-circumscribed nodule with a thin capsule of perineurium that is composed of interlacing bundles of Schwann cells with a characteristic clefting artifact (Figure 2). Cells have wavy dark nuclei with scant cytoplasm that occasionally form palisades or Verocay bodies causing these lesions to be confused with schwannomas. Immunohistochemically, the Schwann cells stain positively with S-100 protein, and the perineurium stains positively with epithelial membrane antigen, Claudin-1, and Glut-1. Neurofilament protein stains axons throughout neuromas, whereas in schwannoma, the expression

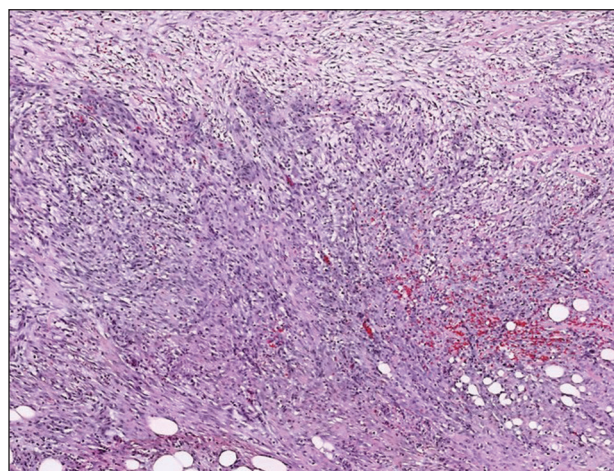


FIGURE 1. Nodular fasciitis. Uniform spindle cells with a tissue culture–like appearance in a loose, myxoid to collagenous stroma (H&E, original magnification $\times 100$).

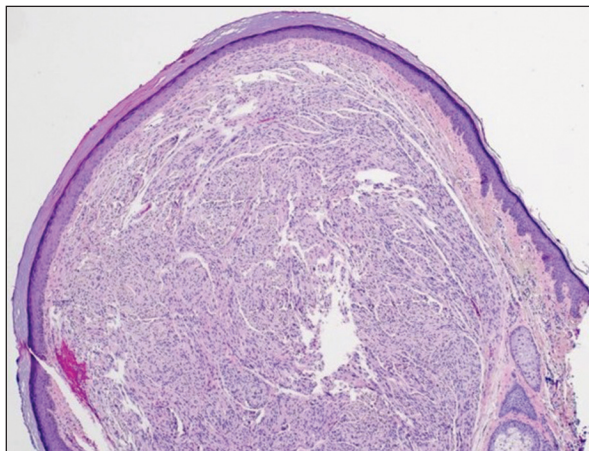


FIGURE 2. Solitary circumscribed neuroma. Interlacing bundles of spindle cells with a characteristic clefting artifact (H&E, original magnification ×40).

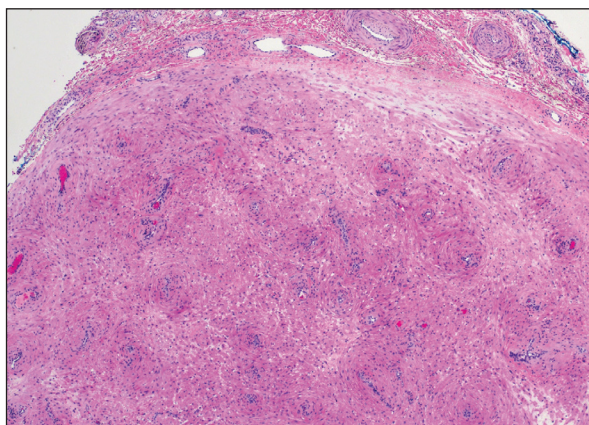


FIGURE 3. Angioleiomyoma. Interlacing, uniform, smooth muscle bundles distributed around vessels (H&E, original magnification ×40).

often is limited to entrapped axons at the periphery of the tumor.⁷

Angioleiomyoma is an uncommon, benign, smooth muscle neoplasm of the skin and subcutaneous tissue that originates from vascular smooth muscle. It most commonly presents in adult females aged 30 to 60 years, with a predilection for the lower limbs. These tumors typically are solitary, slow growing, and less than 2 cm in diameter and may be painful upon compression. Similar to schwannoma, angioleiomyoma is an encapsulated lesion composed of interlacing, uniform, smooth muscle bundles distributed around vessels (Figure 3). Smooth muscle cells have oval- or cigar-shaped nuclei with a small perinuclear vacuole of glycogen. Immunohistochemically, there is strong diffuse staining for smooth muscle actin and h-caldesmon. Recurrence after excision is rare.^{2,8}

Neurofibroma is a common, mostly sporadic, benign tumor of nerve sheath origin. The solitary type may be localized (well circumscribed, unencapsulated) or diffuse. The presence of multiple, deep, and plexiform

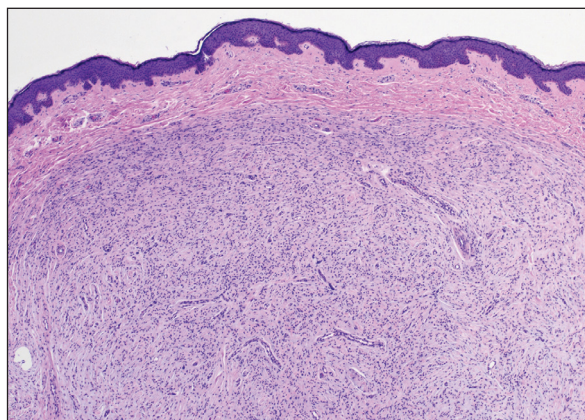


FIGURE 4. Neurofibroma. Loosely arranged spindle cells in a haphazard arrangement with small, hyperchromatic, wavy nuclei in a myxoid to collagenous matrix (H&E, original magnification ×40).

lesions is associated with neurofibromatosis type 1 (von Recklinghausen disease) that is caused by germline mutations in the *NF1* gene. Histologically, the tumor is composed of Schwann cells, fibroblasts, perineurial cells, and nerve axons within an extracellular myxoid to collagenous matrix (Figure 4). The diffuse type is an ill-defined proliferation that entraps adnexal structures. The plexiform type is defined by multinodular serpentine fascicles. Immunohistochemically, the Schwann cells stain positive for S-100 protein and SOX10 (SRY-Box Transcription Factor 10). Epithelial membrane antigen stains admixed perineurial cells. Neurofilament protein highlights intra-tumoral axons, which generally are not found throughout schwannomas. Transformation to a malignant peripheral nerve sheath tumor occurs in up to 10% of patients with neurofibromatosis type 1, usually in plexiform neurofibromas, and is characterized by increased cellularity, atypia, mitotic activity, and necrosis.⁹

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