Soft Tissue Perineurioma of the Finger: Expanding the Differential Diagnosis of a Soft Tissue Tumor Presenting on a Digit

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GOAL

To help recognize and treat patients with perineuriomas

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the presentation of perineuriomas.
2. Describe the variants of perineuriomas.
3. Differentiate perineuriomas from similar conditions.

CME Test on page 215.

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Peripheral nerves are surrounded by an external sheath, which contains concentric layers of thin perineurial cells. Perineuriomas are rare nerve sheath tumors composed of well-differentiated perineurial cells that have a distinct ultrastructural and immunochemical phenotype. We review the histologic characteristics and staining patterns, reported variants, and salient features that differentiate this entity from other soft tissue tumors that may present on a digit. Because of the nonspecific clinical appearance and varying histology on hematoxylin-eosin stain, perineuriomas are likely to be confused with more common tumors of the hand and, therefore, should be included in the differential diagnosis of a soft tissue tumor presenting on a digit.

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Perineurial cells, present in both myelinated and unmyelinated nerves, make up the external sheath, referred to as the *perineurium*, which acts as a perifascicular diffusion barrier for peripheral nerves.[1] Perineuriomas are rare slow-growing tumors composed exclusively of perineurial cells that develop in the dermis, subcutis, or deep soft tissue. Diagnosis relies on the identification of the distinct characteristics of the perineurial cells that compose this tumor. Perineuriomas can arise in various locations and may exhibit several different histologic patterns, all sharing a consistent immunohistochemical and ultrastructural makeup. Familiarity with this entity should help to avoid confusion with more common lesions presenting on a digit, such as a giant cell tumor of the tendon sheath, fibroma of the tendon sheath, neurilemoma, neurofibroma, or sclerotic fibroma. We report 2 cases of soft tissue perineurioma presenting on a digit.

Case Reports

Patient 1—A 13-year-old girl presented with a large, asymptomatic, smooth-surfaced, rubbery-firm reddish yellow nodule on the dorsal mid phalanx of the right third finger that had remained unchanged for 7 years (Figure 1). There was no history of ulceration, infection, or trauma to the area. Results of an x-ray of the right hand revealed soft tissue swelling over the second phalanx with no periosteal reaction.

Results of a biopsy revealed a poorly marginated storiform spindle cell neoplasm involving the dermis and subcutaneous tissue. The base of the proliferation was sharply demarcated centrally, with areas of diffuse infiltration of the adipose tissue peripherally. The spindle cells were uniformly arranged in interweaving fascicles, with portions in a storiform configuration (Figures 2 and 3). Results of immunostains were positive for vimentin and epithelial membrane antigen (EMA) and negative for S-100, HMB-45, melan-A, and desmin (Figure 4). The entire nodule was later removed by an orthopedic surgeon. At 14-month follow-up, the patient reported no evidence of recurrence and a fully functional finger.

Patient 2—A 54-year-old woman with no significant medical history presented with a 4-mm, asymptomatic, firm, skin-colored, smooth-surfaced papule on the dorsal distal phalanx of the left fifth finger. The lesion had been present for 3 to 4 years with no change in appearance. A shave specimen of the exophytic portion of the lesion revealed a fibrotic base that could not be removed with light curettage.

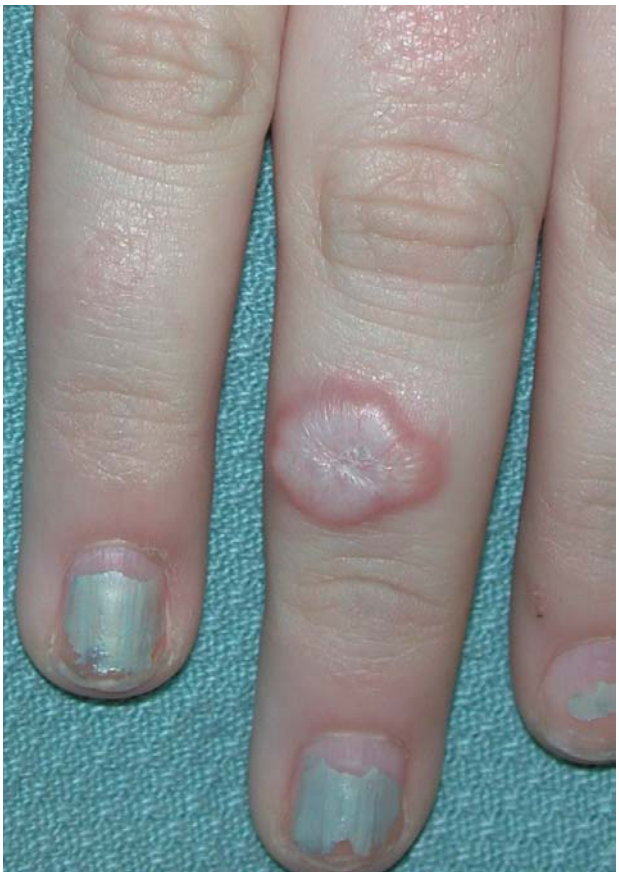

Figure 1. The dorsal right index finger with a well-circumscribed, smooth-surfaced, rubbery-firm, reddish yellow nodule.

Results of histologic evaluation revealed a dome-shaped dermal fibrotic nodule extending to the deep margin of excision. Within the dermis, there was increased deposition of collagen with a proliferation of spindle cells arranged in short fascicles with an ill-defined border. Within the proliferation were foci of cells arranged in a concentric pattern with portions mimicking the appearance of a sclerotic fibroma. No atypia was noted. Results of immunostains were positive for EMA, weakly positive for factor XIIIa, and negative for S-100 and HMB-45. The entire lesion was later removed by a plastic surgeon.

Comment

Perineuriomas result from a proliferation of perineurial cells that normally form the external sheath at the interface between epineurial and endoneurial tissues. These cells have distinct ultrastructural and immunohistochemical phenotypes that comprise a unique component of the normal perineurium. The key diagnostic features include immunoreactivity for EMA with lack of reactivity

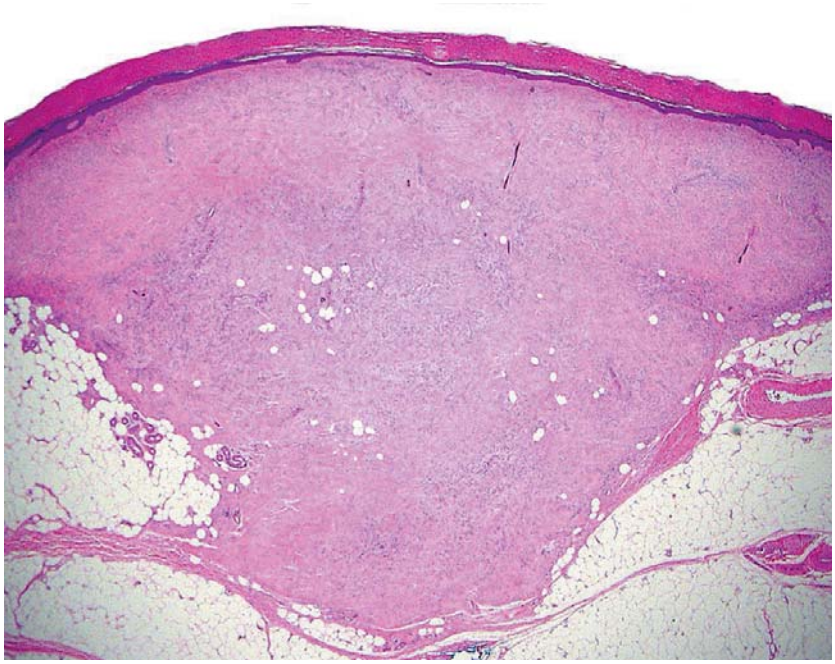

Figure 2. A dermal nodule with a sharply defined base that extends into the subcutaneous tissue (H&E, original magnification ×4).

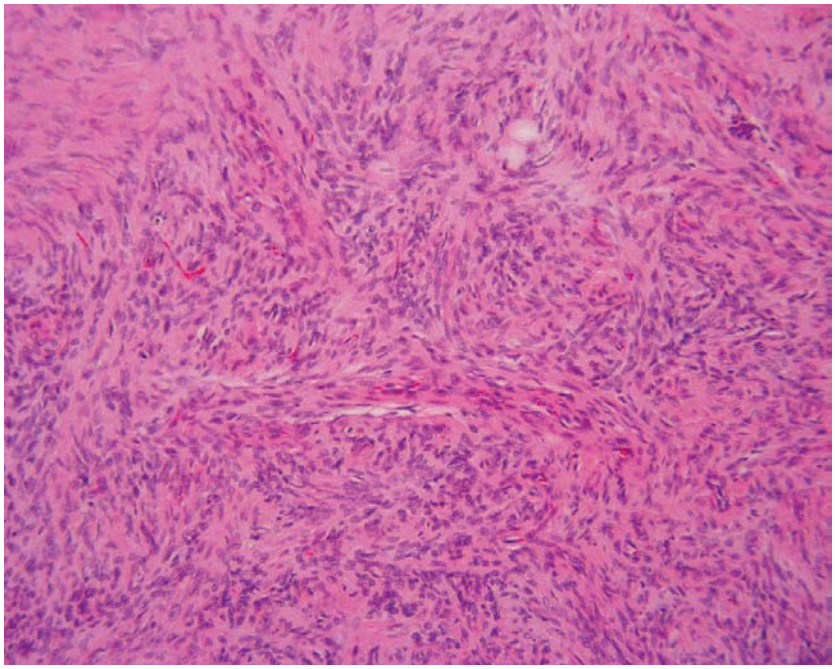

Figure 3. Spindle cells arranged in interweaving fascicles that are relatively uniform and lacking hyperchromasia or pleomorphism (H&E, original magnification ×200).

for S-100. Results of staining for laminin and collagen IV are positive, which can reinforce evidence for perineurial cell differentiation. There are variable staining results for factor XIIIa and CD34,[2] whereas results for cytokeratin and desmin are negative. Ultrastructural features, which may be helpful in confirming the diagnosis, include a discontinuous external lamina, junctional complexes, occasional pinocytotic vesicles, and elongated and spindled cell processes.[3] Identification of a bland spindle cell proliferation on hematoxylin-eosin (H&E) staining, along with the distinct staining profile, form the basis of diagnosing a perineurioma.

Although perineuriomas were originally described by Lazarus and Trombetta in 1978,[4] it was not until the 1999 international consensus conference of neuropathologists that the World Health Organization officially included the perineurioma in its published classification of nervous system tumors.[5] Perineuriomas are rare, invariably benign, peripheral nerve sheath neoplasms with 3 distinct variants established to date: intraneural and extraneural variants, and the more recently described sclerosing perineurioma.[6] The intraneural type extends directly from a peripheral nerve and exhibits a distinct pseudo–onion bulb morphology.[5] The most common presentation is on the extremities of young adults, where it produces a fusiform expansion of the affected nerve. It has been suggested that this may actually represent a reactive process of nerve degeneration rather than a benign free-standing entity.[3]

The extraneural variant, most commonly referred to as *soft tissue perineuriomas*, lack association with an identifiable nerve. This type most closely resembles the original report by Lazarus and Trombetta, subsequently reported in the literature as storiform perineurial fibromas.[7,8] Soft tissue perineuriomas usually present in middle-aged women (female-male ratio, 4:1), with a predilection for the subcutaneous tissue of the extremities or trunk.[5] Several reports describe presentation on digits,

with rare cases describing nail apparatus involvment.[1,9,10] Histologically, the tumors exhibit varied cellularity composed of elongated and spindled cells with a loose storiform, short fascicular, whorled growth pattern.

The sclerosing perineurioma is a recently established variant showing predilection for the digits and palms. Although there is a morphologic overlap with the other forms of perineurioma, the sclerotic variant features plumper, more epithelioid perineurial cells, forming cords and trabecular arrangements embedded in a dense collagen stroma.[3,11] Although not classic, many of these sclerotic features overlap with those of our second case, demonstrating the condition's rich tapestry of presentation. Although each type shows differences in clinical and gross characteristics, all share immunohistochemical and ultrastructural features typical of perineurial cells.[5]

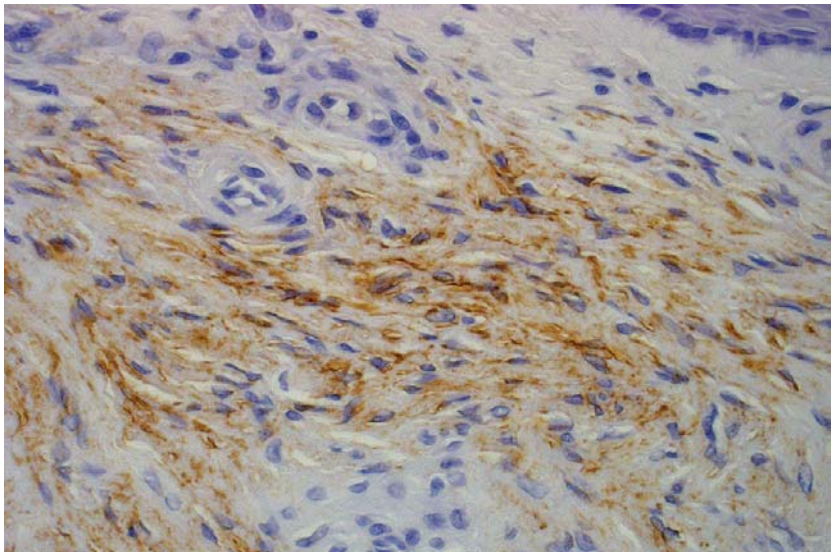

Figure 4. A positive reaction for epithelial membrane antigen (EMA) and a negative reaction for S-100, HMB-45, melan-A, and desmin (EMA, original magnification ×200).

The original case of perineurioma was described on the basis of its ultrastructure; however, distinct immunohistochemical markers that differentiate the perineurioma from more common tumors encountered on a digit are used today. Importantly, immunostains reveal cells to be negative for S-100, differentiating the perineurial cell from the Schwann cell, which is positive for S-100 and negative for EMA. Both the neurilemoma and the neurofibroma show reactivity for S-100. The diagnosis of giant cell tumor of the tendon sheath is usually characterized by the presence of osteoclastlike giant cells, but these markers may be subtle or entirely absent. The absence of EMA activity, also lacking in fibroma of the tendon sheath, helps to differentiate giant cell tumor of the tendon sheath from perineurioma in this scenario.[1] A calcifying aponeurotic fibroma also could potentially be confused with a perineurioma, but the absence of cartilage or calcification, and reactivity for vimentin only, would differentiate the 2 entities.[1] Multiple sclerotic fibromas may serve as a cutaneous marker for Cowden disease. These well-demarcated dermal nodules with thick hyalinized collagen bundles with a storiform and whorled architecture may be confused with the perineurioma, especially those of the sclerotic variant. The sclerotic fibromas of Cowden disease, though positive for factor XIIIa and collagen IV, are negative for laminin and EMA.

Because EMA expression is a key to the diagnosis of perineurioma, and because at times the reactivity may be focal or faint, additional markers specific to perineurial cells are of particular interest. In a recent report on a group of tight junction-associated proteins, it was noted that perineurial cells expressed high levels of claudin-1. Folpe et al[12] showed expression of claudin-1 in 11 of 12 cases of perineurioma, of which the majority showed a higher reactivity for claudin-1 staining compared with the corresponding EMA stain. Importantly, claudin-1 is not expressed in the mesenchymal tumors that may enter into the differential diagnosis of perineurioma. Claudin-1 may serve as a valuable adjunct to EMA in cases with less than classic characteristics.

Several reports have described genetic abnormalities that serve as a common denominator within the perineurioma spectrum. Giannini et al[7] postulated that soft tissue perineurioma exhibited the same chromosome 22 abnormalities found in intraneural variants. The researchers conducted a fluorescent in situ hybridization experiment with a probe specific for the *M-BCR* locus, which maps chromosome band 22q11, and found that 4 out of 5 cases tested showed deletion of part of chromosome 22.[7] Recently, similar abnormalities were found in the sclerosing variant. Sciot et al,[13] using 2 markers for the *5'BCR* and the *NF2* loci, both on chromosome 22, showed cryptic deletion of these loci, further

supporting that a gene on chromosome 22 may play a role in the pathogenesis of perineurioma. Because of its involvement in other nerve sheath tumors, the *NF2* gene is a logical candidate.

Excision with a thin margin of normal tissue is curative. Due to the nonspecific clinical appearance and varying histologic morphology, the perineurioma is likely to be confused with more common tumors of the hand. Further investigation is needed to learn more about new variants of perineurioma, more specific immunostains for use in diagnosis, and identification of specific genes that are a key to the condition's pathogenesis. Perineurioma joins the more commonly recognized giant cell tumor of the tendon sheath, fibroma of the tendon sheath, neurilemoma, neurofibroma as a soft tissue tumor, and sclerosing fibroma that may present on a digit.

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