Cutaneous and Subcutaneous Perineuriomas in 2 Pediatric Patients

Priscilla R. Lyon, DO; Brooke Burgess, MS; Elyssa A. Berg, MD, MPH; Martin P. Fernandez, MD; Debby Rampisela, MD

PRACTICE **POINTS**

- Perineuriomas are rare benign peripheral nerve sheath tumors that most commonly occur in young to middle-aged adults but rarely can present in children.
- Immunohistochemically, perineuriomas show positive staining with epithelial membrane antigen, GLUT1, claudin-1, and frequently with CD34; they are negative for S-100 and glial fibrillary acidic protein.
- Perineuriomas should be considered in the differential diagnosis in children who present with a well-circumscribed nodular lesion in the subcutaneous tissue.

Perineuriomas are rare benign peripheral nerve sheath tumors that can present in a variety of locations with varying histologic patterns, most commonly in young to middle-aged adults; they are particularly rare in the pediatric population. Perineuriomas have a distinctive constellation of morphologic, immunohistochemical, and ultrastructural characteristics that allows for distinction from other benign peripheral nerve sheath tumors. We present 2 cases of perineuriomas that arose as cutaneous lesions in children.

Cutis. 2022;110:277-280.

Perineuriomas are benign, slow-growing tumors derived from perineurial cells,[1] which form the structurally supportive perineurium that surrounds individual nerve fascicles.[2,3] Perineuriomas are classified into 2 main forms: intraneural or extraneural.[4] Intraneural perineuriomas are found within the border of the peripheral nerve,[5] while extraneural perineuriomas usually are found in soft tissue and skin. Extraneural perineuriomas can be further classified into variants based on their histologic appearance, including reticular, sclerosing, and plexiform subtypes. Extraneural perineuriomas usually present on the extremities or trunk of young to middle-aged adults as a well-circumscribed, painless, subcutaneous masses.[1] These tumors are especially unusual in children.[4] We present 2 extraneural perineurioma cases in children, and we review the pertinent diagnostic features of perineurioma as well as the presentation in the pediatric population.

Case Reports

Patient 1—A 10-year-old boy with a history of cerebral palsy and related comorbidities presented to the clinic for evaluation of a lesion on the thigh with no associated pain, irritation, erythema, or drainage. Physical examination revealed a soft, pedunculated, mobile nodule on the right medial thigh. An elliptical excision was performed. Gross examination demonstrated a 2.0×2.0×1.8-cm polypoid nodule. Histologic examination showed a dermal-based proliferation of bland spindle cells (Figure 1). The cytomorphology was characterized by elongated tapering nuclei and many areas with delicate bipolar cytoplasmic processes. The constituent cells were arranged in a whorled pattern in a variably myxoid to collagenous stroma. The tumor cells were multifocally positive for CD34; focally positive for smooth muscle actin (SMA); and negative for S-100, epithelial membrane antigen (EMA), GLUT1, claudin-1, STAT6, and desmin. Rb protein was intact. The CD34 immunostain highlighted the cytoplasmic processes. Electron microscopy was performed because the immunohistochemical results were nonspecific despite the favorable histologic features for perineurioma and showed pinocytic vesicles with

Drs. Lyon, Fernandez, and Rampisela are from the Department of Pathology, Baylor Scott & White Health, Temple, Texas. Ms. Burgess is from Texas A&M College of Medicine, Dallas. Dr. Berg is from the Division of Internal Medicine and Health Services Research, University of California, Los Angeles.

The authors report no conflict of interest.

Correspondence: Martin P. Fernandez, MD, 2401 S 31st St, Temple, TX 76508 (martin.fernandez@bswhealth.org).

doi:10.12788/cutis.0644

delicate cytoplasmic processes, characteristic of perineurioma (Figure 2). Follow-up visits were related to the management of multiple comorbidities; no known recurrence of the lesion was documented.

Patient 2—A 15-year-old adolescent boy with no notable medical history presented to the pediatric clinic for a bump on the right upper arm of 4 to 5 months' duration. He did not recall an injury to the area and denied change in size, redness, bruising, or pain of the lesion. Ultrasonography demonstrated a 2.6×2.3×1.3-cm hypoechoic and slightly heterogeneous, well-circumscribed, subcutaneous mass with internal vascularity. The patient was then referred to a pediatric surgeon. The clinical differential included a lipoma, lymphadenopathy, or sebaceous cyst. An excision was performed. Gross inspection demonstrated a 7-g, 2.8×2.6×1.8-cm, homogeneous, tan-pink, rubbery nodule with minimal surrounding soft tissue. Histologic examination showed a bland proliferation of spindle cells with storiform and whorled patterns (Figure 3). No notable nuclear atypia or necrosis was identified. The tumor cells were focally positive for EMA (Figure 4), claudin-1, and CD34 and negative for S-100, SOX10, GLUT1, desmin, STAT6, pankeratin AE1/AE3, and SMA. The diagnosis of perineurioma was rendered. No recurrence of the lesion was appreciated clinically on a 6-month follow-up examination.

Comment

Characteristics of Perineuriomas—On gross evaluation, perineuriomas are firm, gray-white, and well circumscribed but not encapsulated. Histologically, perineuriomas can have a storiform, whorled, or lamellar pattern of spindle cells. Perivascular whorls can be a histologic clue. The spindle cells are bland appearing and typically are elongated and slender but can appear slightly ovoid and plump. The background stroma can be myxoid, collagenous, or mixed. There usually is no atypia, and mitotic figures are rare.[2,3,6,7] Intraneural perineuriomas vary architecturally in that they display a unique onion bulb–like appearance in which whorls of cytoplasmic material of variable sizes surround central axons.[3]

Diagnosis—The diagnosis of perineuriomas usually requires characteristic immunohistochemical and sometimes ultrastructural features. Perineuriomas are positive for EMA and GLUT1 and variable for CD34.[6] Approximately 20% to 91% will be positive for claudin-1, a tight junction protein associated with perineuriomas.[8] Of note, EMA and GLUT1 usually are positive in both neoplastic and nonneoplastic perineurial cells.[9,10] Occasionally, these tumors can be focally positive for SMA and negative for S-100 and glial fibrillary acidic protein. The bipolar, thin, delicate, cytoplasmic processes with long-tapering nuclei may be easier to appreciate on electron microscopy than on conventional light microscopy. In addition, the cells contain pinocytotic vesicles and a discontinuous external lamina, which may be helpful for diagnosis.[10]

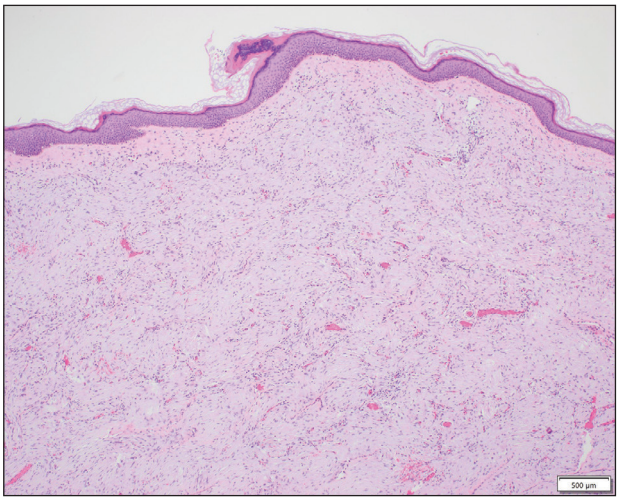

FIGURE 1. Proliferation of spindle cells involving the reticular dermis (H&E, original magnification ×200). Reference bar indicates 500 µm.

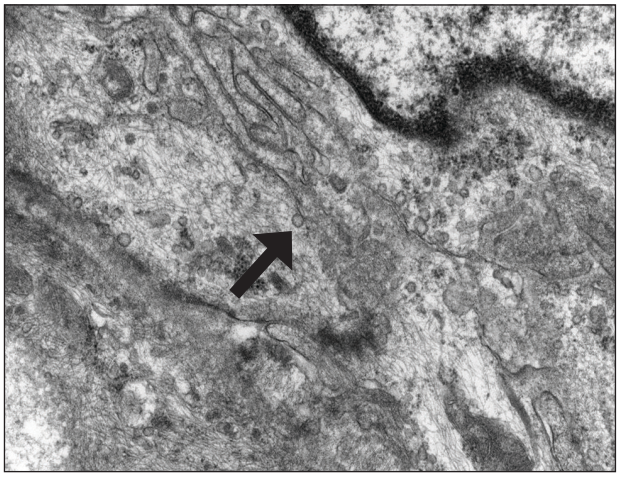

FIGURE 2. Electron microscopy showed long, slender, cytoplasmic processes coated by discontinuous basal lamina and the presence of many pinocytic vesicles (black arrow)(original magnification ×15,000).

Genetics—Genetic alterations in perineurioma continue to be elucidated. Although many soft tissue perineuriomas possess deletion of chromosome 22q material, this is not a consistent finding and is not pathognomonic. Notably, the *NF2* tumor suppressor gene is found on chromosome 22.[11] For the sclerosing variant of perineurioma, rearrangements or deletions of chromosome 10q have been described. A study of 14 soft tissue/extraneural perineuriomas using whole-exome sequencing and single nucleotide polymorphism array showed 6 cases of recurrent chromosome 22q deletions containing the *NF2* locus and 4 cases with a previously unreported finding of chromosome 17q deletions containing the *NF1* locus that were mutually exclusive events in all but 1 case.[12] Although perineuriomas can harbor *NF1* or *NF2* mutations, perineuriomas are not considered to be associated with

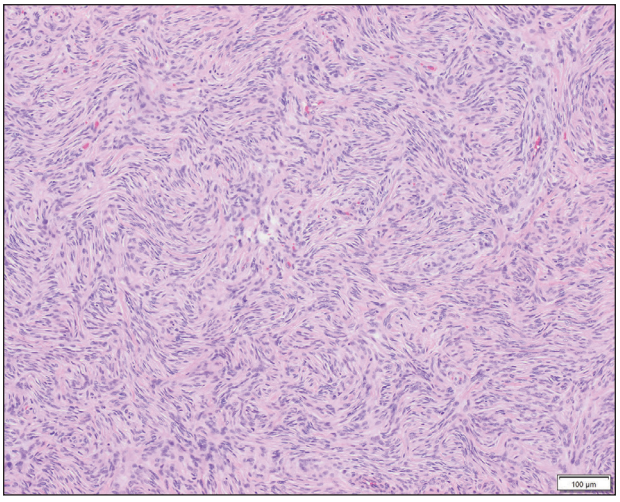

FIGURE 3. Spindle cell proliferation with storiform and whorled patterns (H&E, original magnification ×100). Reference bar indicates 100 µm.

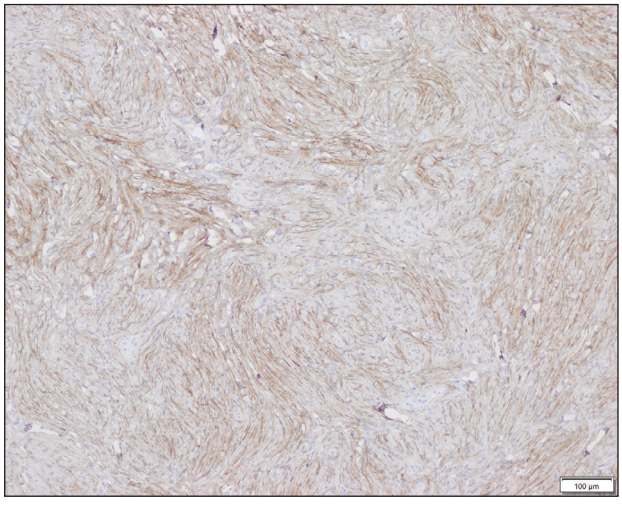

FIGURE 4. Immunohistochemistry revealed epithelial membrane antigen positivity in spindle cells (original magnification ×100). Reference bar indicates 100 µm.

neurofibromatosis type 1 or 2 (NF1 or NF2, respectively). Patients with NF1 or NF2 and perineurioma are exceedingly rare. One pediatric patient with both soft tissue perineurioma and NF1 has been reported in the literature.[13]

Differential Diagnosis—Perineuriomas should be distinguished from other benign neural neoplasms of the skin and soft tissue. Commonly considered in the differential diagnosis is schwannoma and neurofibroma. Schwannomas are encapsulated epineurial nerve sheath tumors comprised of a neoplastic proliferation of Schwann cells. Schwannomas morphologically differ from perineuriomas because of the presence of the hypercellular Antoni A with Verocay bodies and the hypocellular myxoid Antoni B patterns of spindle cells with elongated wavy nuclei and tapered ends. Other features include hyalinized vessels, hemosiderin deposition, cystic degeneration, and/or degenerative atypia.[3,14] Importantly, the constituent cells of schwannomas are positive for S-100 and SOX10 and negative for EMA.[3] Neurofibromas consist of fascicles and whorls of Schwann cells in a background myxoid stroma with scattered mast cells, lymphocytes, fibroblasts, and perineurial cells. Similar to schwannomas, neurofibromas also are positive for S-100 and negative for EMA.[3,14] Neurofibromas can have either a somatic or germline mutation of the biallelic *NF1* gene on chromosome 17q11.2 with subsequent loss of protein neurofibromin activity.[15] Less common but still a consideration are the hybrid peripheral nerve sheath tumors that may present with a biphasic or intermingled morphology. Combinations include neurofibroma-schwannoma, schwannoma-perineurioma, and neurofibroma-perineurioma. The hybrid schwannoma-perineurioma has a mixture of thin and plump spindle cells with tapered nuclei as well as patchy S-100 positivity corresponding to schwannian areas. Similarly, S-100 will highlight the wavy Schwann cells in neurofibroma-perineurioma as well as CD34-highlighting fibroblasts.[7,15] In both aforementioned hybrid tumors, EMA will be positive in the perineurial areas. Another potential diagnostic consideration that can occur in both pediatric and adult populations is dermatofibrosarcoma protuberans (DFSP), which is comprised of a dermal proliferation of monomorphic fusiform spindle cells. Although both perineuriomas and DFSP can have a storiform architecture, DFSP is more asymmetric and infiltrative. Dermatofibrosarcoma protuberans is recognized in areas of individual adipocyte trapping, referred to as *honeycombing*. Dermatofibrosarcoma protuberans typically does not express EMA, though the sclerosing variant of DFSP has been reported to sometimes demonstrate focal EMA reactivity.[11,14,16] For morphologically challenging cases, cytogenetic studies will show t(17;22) translocation fusing the *COL1A1* and *PDGFRB* genes.[16] Finally, for subcutaneous or deep-seated tumors, one also may consider other mesenchymal neoplasms, including solitary fibrous tumor, low-grade fibromyxoid sarcoma, or low-grade malignant peripheral nerve sheath tumor (MPNST).[11]

Management—Perineuriomas are considered benign. The presence of mitotic figures, pleomorphism, and degenerative nuclear atypia akin to ancient change, as seen in ancient schwannoma, does not affect their benign clinical behavior. Treatment of a perineurioma typically is surgical excision with conservative margins and minimal chance of recurrence.[1,11] So-called malignant perineuriomas are better classified as MPNSTs with perineural differentiation or perineurial MPNST. They also are positive for EMA and may be distinguished from perineurioma by the presence of major atypia and an infiltrative growth pattern.[17,18]

Considerations in the Pediatric Population—Few pediatric soft tissue perineuriomas have been reported. A clinicopathologic analysis by Hornick and Fletcher[1] of patients with soft tissue perineurioma showed that only 6 of 81 patients were younger than 20 years. The youngest reported case of perineurioma occurred as an extraneural

perineurioma on the scalp in an infant.[19] Only 1 soft tissue perineural MPNST has been reported in the pediatric population, arising on the face of an 11-year-old boy. In a case series of 11 pediatric perineuriomas, including extraneural and intraneural, there was no evidence of recurrence or metastasis at follow-up.[4]

Conclusion

Perineuriomas are rare benign peripheral nerve sheath tumors with unique histologic and immunohistochemical features. Soft tissue perineuriomas in the pediatric population are an important diagnostic consideration, especially for the pediatrician or dermatologist when encountering a well-circumscribed nodular soft tissue lesion of the extremity or when encountering a neural-appearing tumor in the subcutaneous tissue.

Acknowledgment—We would like to thank Christopher Fletcher, MD (Boston, Massachusetts), for his expertise in outside consultation for patient 1.

REFERENCES

1. Hornick J, Fletcher C. Soft tissue perineurioma. *Am J Surg Pathol*. 2005;29:845-858.
2. Tsang WY, Chan JK, Chow LT, et al. Perineurioma: an uncommon soft tissue neoplasm distinct from localized hypertrophic neuropathy and neurofibroma. *Am J Surg Pathol*. 1992;16:756-763.
3. Belakhoua SM, Rodriguez FJ. Diagnostic pathology of tumors of peripheral nerve. *Neurosurgery*. 2021;88:443-456.
4. Balarezo FS, Muller RC, Weiss RG, et al. Soft tissue perineuriomas in children: report of three cases and review of the literature. *Pediatr Dev Pathol*. 2003;6:137-141. Published correction appears in *Pediatr Dev Pathol*. 2003;6:following 364.
5. Macarenco R, Ellinger F, Oliveira A. Perineurioma: a distinctive and underrecognized peripheral nerve sheath neoplasm. *Arch Pathol Lab Med*. 2007;131:625-636.
6. Agaimy A, Buslei R, Coras R, et al. Comparative study of soft tissue perineurioma and meningioma using a five-marker immunohistochemical panel. *Histopathology*. 2014;65:60-70.
7. Greenson JK, Hornick JL, Longacre TA, et al. *Sternberg's Diagnostic Surgical Pathology.* Wolters Kluwer; 2015.
8. Folpe A, Billings S, McKenney J, et al. Expression of claudin-1, a recently described tight junction-associated protein, distinguishes soft tissue perineurioma from potential mimics. *Am J Surg Pathol*. 2002;26:1620-1626.
9. Hirose T, Tani T, Shimada T, et al. Immunohistochemical demonstration of EMA/Glut1-positive perineurial cells and CD34-positive fibroblastic cells in peripheral nerve sheath tumors. *Mod Pathol*. 2003;16:293-298.
10. Fletcher CDM, Bridge JA, Hogendoorn PCW, et al. Perineurioma. *WHO Classification of Tumours of Soft Tissue and Bone.* IARC Press; 2013:176-178.
11. Hornick JL. *Practical Soft Tissue Pathology: A Diagnostic Approach.* Elsevier Saunders; 2013.
12. Carter JM, Wu Y, Blessing MM, et al. Recurrent genomic alterations in soft tissue perineuriomas. *Am J Surg Pathol*. 2018;42:1708-1714.
13. Al-Adnani M. Soft tissue perineurioma in a child with neurofibromatosis type 1: a case report and review of the literature. *Pediatr Dev Pathol*. 2017;20:444-448.
14. Reddy VB, David O, Spitz DJ, et al. *Gattuso's Differential Diagnosis in Surgical Pathology.* Elsevier Saunders; 2022.
15. Michal M, Kazakov DV, Michal M. Hybrid peripheral nerve sheath tumors: a review. *Cesk Patol*. 2017;53:81-88.
16. Abdaljaleel MY, North JP. Sclerosing dermatofibrosarcoma protuberans shows significant overlap with sclerotic fibroma in both routine and immunohistochemical analysis: a potential diagnostic pitfall. *Am J Dermatopathol*. 2017;39:83-88.
17. Rosenberg AS, Langee CL, Stevens GL, et al. Malignant peripheral nerve sheath tumor with perineurial differentiation: "malignant perineurioma." *J Cutan Pathol*. 2002;29:362-367.
18. Mitchell A, Scheithauer BW, Doyon J, et al. Malignant perineurioma (malignant peripheral nerve sheath tumor with perineural differentiation). *Clin Neuropathol*. 2012;31:424-429.
19. Duhan A, Rana P, Beniwal K, et al. Perineurioma of scalp in an infant: a case report with short review of literature. *Asian J Neurosurg*. 2016;11:81-83.