Myxoid perineurioma: an entity with many mimics

Seo Hyun Kim[1] BA, Kiley Fagan[2] MD, Susan B Dorsey[2] MD, Douglas J Grider[2-4] MD

Affiliations: [1]Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA, [2]Dermatology Section, Department of Internal Medicine, Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA, [3]Department of Basic Science Education, Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA, [4]Dominion Pathology Associates, Roanoke Virginia, USA

Corresponding Authors: Seo Hyun Kim BA, 131 Campbell Avenue SW, Roanoke, VA 24011, Tel: 312-636 5352, Email: elinak@vt.edu; Douglas J Grider MD, 1 Riverside Circle, Roanoke, VA 24016, Tel: 540-352-0976, Email: djgrider@carilionclinic.org

Abstract

We present a case of a female patient who presented with a 0.6cm flesh-colored "rubbery" papule on the left thigh. Biopsy revealed a dermal myxoid tumor containing spindled cells, tapered nuclei, indistinct cell borders, and a large number of mast cells. The spindle cells stained negative for S100 protein and Sox10 on immunohistochemistry, excluding myxoid neurofibroma, but positive for epithelial membrane antigen (EMA), and CD34, supporting a diagnosis of myxoid perineurioma. Interestingly, the mast cells showed cytoplasmic and nuclear positivity for microphthalmia transcription factor (MiTF). The lesion was fully excised one year later with identical histopathology and ancillary immunohistochemical profile.

Keywords: mast cells, myxoid perineurioma, neurofibroma

Introduction

Perineuriomas are rare benign peripheral nerve sheath tumors that only account for about one percent of all soft tissue neoplasms [1,2]. Extraneural perineuriomas can grow in various patterns and contain myxoid, collagenous stroma, or both [3]. Histopathological findings usually reveal spindle cells which have wavy or tapering nuclei, an eosinophilic nucleolus, and indistinct cell borders. Immunohistochemical staining is typically positive for epithelial membrane antigen (EMA) and negative for S100 and Sox10 [3]. Diagnosis of myxoid perineurioma is challenging and underreported, as it can mimic other dermatologic entities such as myxoid neurofibroma, myxoid dermatofibroma, and myxoid dermatofibrosarcoma protuberans (DSFP). Although it is well known that mast cells are seen in high frequencies in neurofibromas, they are also seen in other nerve sheath tumors and soft tissue sarcomas, including perineurioma [4,5]. We describe a rare case of an 81-year-old woman with an extraneural myxoid perineurioma that mimicked many other dermatologic etiologies and interestingly, showed mast cells with both nuclear and cytoplasmic microphthalmia transcription factor (MiTF) positivity. This case highlights the importance of recognizing MiTF-positive mast cells in perineuriomas and the various immunohistochemical findings necessary to arrive at the correct diagnosis.

Case Synopsis

An 81-year-old woman presented with a 0.6cm flesh-colored "rubbery" papule located on the left upper posterior lateral thigh (**Figure 1**). Punch biopsy revealed a dermal myxoid lesion containing spindled cells with tapered nuclei without distinct cell borders associated with large numbers of mast cells (**Figure 2A, B**). S100 protein and Sox10 immunohistochemical stains were negative in the spindle cells, excluding the expected diagnosis of myxoid neurofibroma (**Figure 3A, B**). Factor XIIIa was negative, excluding myxoid dermatofibroma. Epithelial membrane antigen and CD34 were positive, supporting a diagnosis of myxoid perineurioma (**Figures 3C, D**). GLUT1 and claudin 1

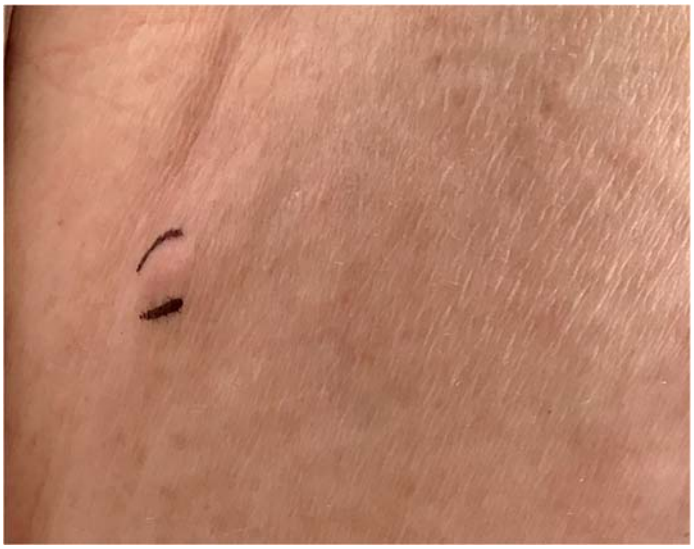

Figure 1. *Left upper posterior thigh flesh colored papule (0.6cm).*

were both negative, as can be seen in a significant number of perineuriomas but can be helpful for confirmation when present. Myxoid dermatofibrosarcoma protuberans was excluded by the EMA positivity. The considered differential diagnoses and their respective immunohistochemical stain findings are summarized (**Table 1**). Interestingly, the mast cells showed cytoplasmic and some nuclear positivity for nuclear MiTF (**Figure 4A**), in addition to the expected cytoplasmic Giemsa positivity (**Figure 4B**). The lesion was fully excised one year later with identical histopathology, ancillary immunohistochemical profile, and associated scar secondary to the prior procedure (**Figure 5A, B**).

Case Discussion

First described by Lazarus and Trombetta in 1978, perineuriomas are uncommon benign peripheral nerve sheath tumors that are comprised of perineural cells [1,2]. Perineural cells line the perineurium, a barrier located between the epineurium and endoneurium of peripheral nerve axons [6]. At first glance, the histopathology in this case showed an uncircumscribed, spindle cell proliferation in a myxoid stroma with scattered Giemsa-positive mast cells. These histologic features favored a diagnosis of myxoid neurofibroma. However, S100 and Sox10 by immunohistochemistry were negative, excluding a Schwann cell proliferation, such as a neurofibroma or Schwannoma. Melanocyte proliferations such as perineuriomatous melanocytic nevus were also unlikely given negative S100 and Sox10 [7]. A negative Factor XIIIa excluded a myxoid dermatofibroma. Early myxoid DSFP was considered, but a positive EMA favored a diagnosis of myxoid perineurioma. GLUT1 and claudin 1 were negative, as is often the case in perineuriomas, but if positive can

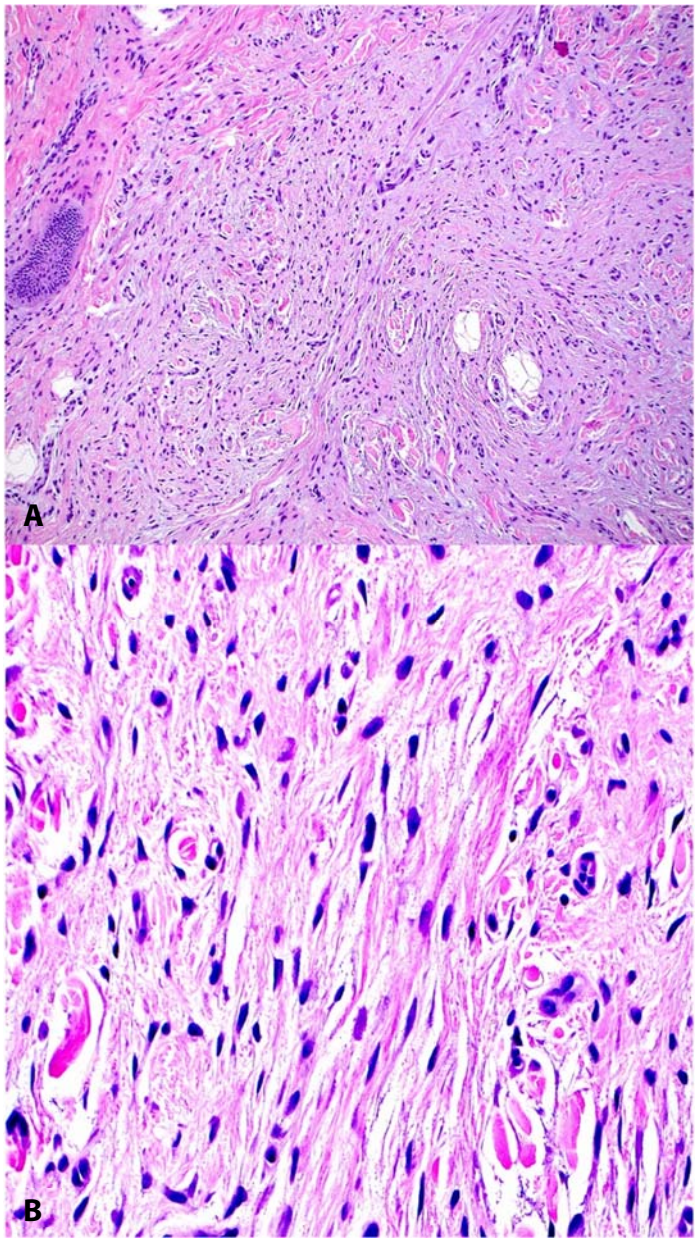

Figure 2. *H&E histopathology showing **A)** spindled cells with tapered nuclei and indistinct cell borders in myxoid stroma, 10×; **B)** spindled cells with tapered nuclei and indistinct cell borders in myxoid stroma, 40×.*

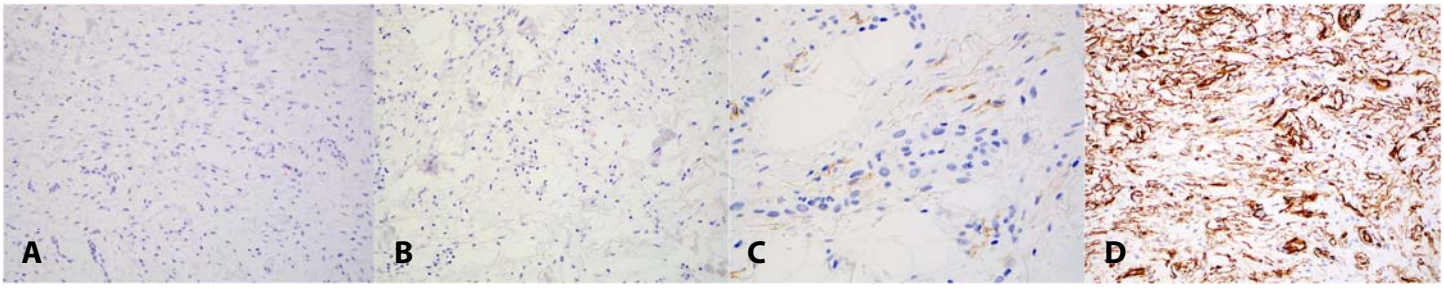

Figure 3. *Immunohistochemistry profiling: A, **B)** Spindled cells are both S100 protein (40X×) and Sox10 negative (20×), respectively; **C)** Spindled cells are EMA positive (40×); **D)** Spindled cells and blood vessels are CD34 positive (40×).*

be supportive of a diagnosis of perineurioma [3,8-10].

Perineuriomas are traditionally categorized into intraneural or extraneural (soft tissue) variants. Intraneural perineuriomas are characterized by neoplastic perineural cells that proliferate throughout the endoneurium [11] and create a characteristic pseudo-onion bulb morphology [12]. In comparison, extraneural perineuriomas are neoplastic perineural cell proliferations that are not grossly associated with a nerve. Extraneural perineuriomas are more common than intraneural

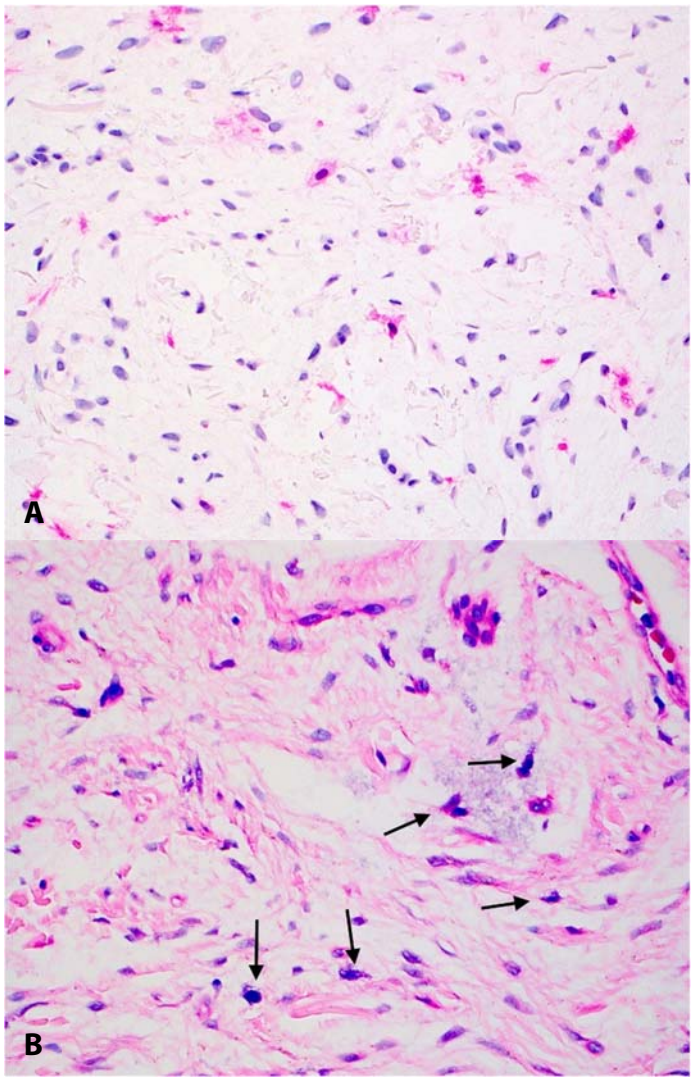

Figure 4. ***A)*** *Mast cells have cytoplasmic MiTF positivity, 40×.* ***B)*** *Mast cells noted by arrows show magenta cytoplasmic granules on Giemsa, 40×.*

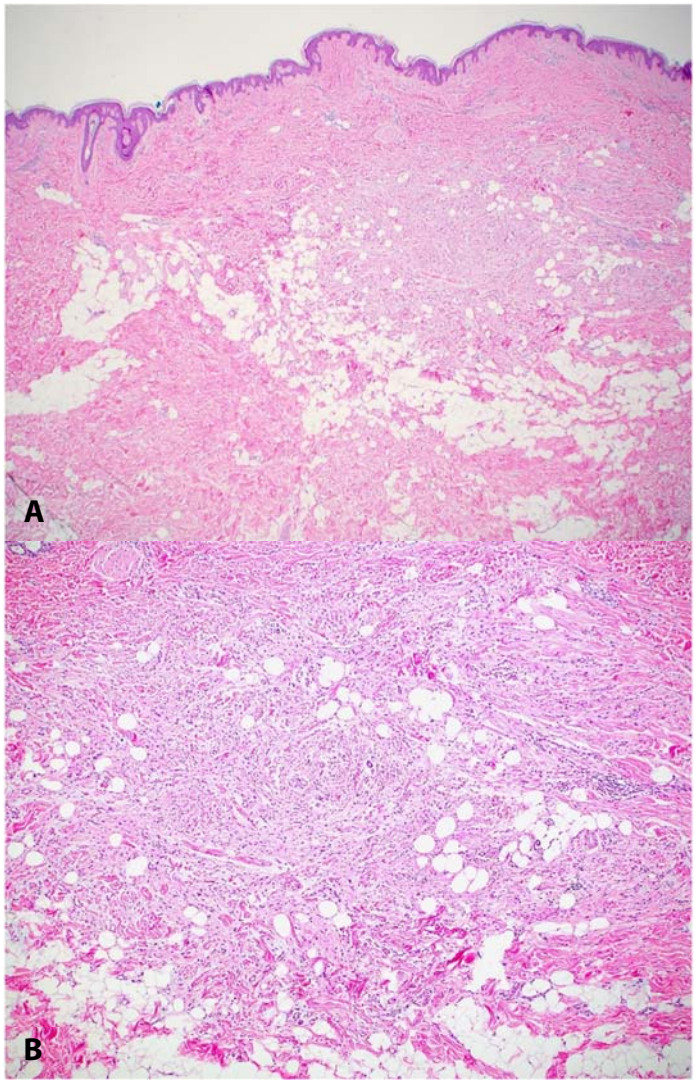

Figure 5. *Excision of myxoid perineurioma, H&E,* ***A)*** *2×,* ***B)*** *4×.*

Table 1. *Summary of the differential diagnoses and their associated immunohistochemical staining findings [6,25,26,29,30-33].*

	S100	Sox10	Factor XIIIa	EMA	CD34	GLUT1	Claudin 1
Myxoid perineurioma	–	–	–	+	+/–	+/–	+/–
Myxoid neurofibroma	+	+	+/–	–	+	–	–
Myxoid dermatofibroma	–	–	+	–	–	–	–
Myxoid dermatofibrosarcoma protuberans	–	–	–	–	+	–	–

perineuriomas [12] and will be the primary subject of discussion in this report.

Extraneural perineuriomas generally present as a solitary, small (mostly <10cm), firm, and well-circumscribed but not encapsulated, painless mass or nodule [12,13]. Grossly, the tumors are usually white-to-gray in color [12]. They most commonly arise in the subcutaneous tissue of the trunk and extremities, particularly the hands. However, some examples have also been described in the head and neck area, retroperitoneum [8], brain, kidney, and intestines [14]. They usually affect adults, although some cases have been reported in children [15]. Recent studies have shown that there is no sex predilection except for the sclerosing type which most often occurs in the fingers of young males [16].

Extraneural perineuriomas can grow in various patterns, including storiform (most common), lamellar, whorled, Pacinian, or fascicular [12,16]. The tumor most commonly contains collagenous stroma, although myxoid stroma, or a mixed collagenous-myxoid stroma pattern can also be seen [3]. Perineuriomas can be hypocellular or hypercellular in appearance, reflecting a scarce or abundant intercellular matrix, respectively [9,17]. They usually involve spindle cells which have wavy or tapering nuclei, an eosinophilic nucleolus, and indistinct cell borders. Oftentimes, perivascular whorls are seen [12]. Mitotic activity and degenerative atypia may be present; however, necrosis is usually absent.

There are two main variants of extraneural perineurioma: sclerosing perineurioma and reticular perineurioma. Sclerosing perineurioma contains small, plump spindled and epithelioid tumor cells in a dense collagenous stroma. There are prominent thin-walled vessels, around which the tumor cells arrange in a lace-like pattern [12,16]. Reticular perineuriomas also contain tumor cells that arrange in a lace-like reticular pattern, but they contain degenerative myxoid changes and may form pseudocystic spaces [12,18]. Other histopathologic perineurioma variants have been reported, including perineurioma with granular cells [19], perineurioma with adipocytes [20], perineurioma with ossification [21], and plexiform perineurioma [22].

Immunohistochemical staining of perineurioma is typically positive for EMA and negative for S100 and Sox10 [3]. They are also sometimes positive for collagen type IV, laminin, vimentin, CD34, smooth muscle actin (SMA), GLUT1, and claudin 1 [3,8-10,12]. Studies have reported immunohistochemistry sensitivities of 93 to 100% for EMA, 63% for GLUT1, 29 to 90% for claudin 1, 21% for SMA, and 5% for S100 in detecting perineuriomas [8,23].

Although it is well known that mast cells are seen in high frequencies in neurofibromas, they are also seen in other nerve sheath tumors and soft tissue sarcomas, including perineurioma [4,5]. Donhuijsen et al. evaluated 164 tumors and found that 70% of neurofibromas had very high mast cell counts. However other tumors including malignant schwannomas, malignant fibrous histiocytomas, and leiomyosarcomas had remarkably high mast cell counts as well. Of note, the number of mast cells has been correlated positively to the amount of myxoid and collagenous connective tissue [4]. Mast cells have been seen in perineuriomas of other sites as well [5] and are frequently seen in sclerosing perineurioma [12,24]. Interestingly, the Giemsa positive mast cells in this case were positive for microphthalmia transcription factor (MiTF), a nuclear stain, by immunohistochemistry. Although nuclear MiTF positivity of mast cells has been well-documented in systemic mastocytosis, its role in perineuriomas remains poorly understood [25,26].

Furthermore, the mast cells in our case demonstrated not only nuclear positivity but also cytoplasmic positivity for MiTF by immunohistochemistry. The significance of this is uncertain, but this case highlights the importance of recognizing mast cells in spindled cell proliferations other than neurofibromas.

The exact etiology of perineuriomas is unknown. However, cytogenetic studies have revealed that patients with both intraneural and extraneural perineuriomas have chromosome 22 abnormalities, particularly deletion or monosomy of the 22q11~q13.1 regions [11]. Perineuriomas are benign and rarely recur, although rare cases of sporadic tumors have been reported in patients with neurofibromatosis type 1 or 2 [27,28]. They are usually cured by surgical resection with negative margins.

Conclusion

This case demonstrates an uncommon but likely underreported entity in dermatopathology, a perineurioma. The difficulty in establishing this diagnosis lay with its mimic, a myxoid neurofibroma, due to the similar architecture and presence of mast cells. However, immunohistochemical staining with positivity for EMA and negativity for S100 and Sox-10 helped secure the diagnosis of perineurioma. Pathologists and dermatopathologists should be aware that the presence of mast cells in a spindled, neural neoplasm does not secure the diagnosis of neurofibroma.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Lazarus SS, Trombetta LD. Ultrastructural identification of a benign perineurial cell tumor. *Cancer*. 1978;41:1823-9. [PMID: 647630].
2. Rodriguez FJ, Folpe AL, Giannini C, Perry A. Pathology of peripheral nerve sheath tumors: diagnostic overview and update on selected diagnostic problems. *Acta Neuropathol*. 2012;123:295-319. [PMID: 22327363].
3. Shanthaveerappa TR, Bourne GH. Perineural epithelium: a new concept of its role in the integrity of the peripheral nervous system. *Science*. 1966;154:1464-7. [PMID: 5921613].
4. McCalmont TH, Emanuel B, Fung M, Ruben BS. Perineuriomatous melanocytic nevi. *J Cutan Pathol*. 2011;38:940-2. [PMID: 22050089].
5. Ariza A, Bilbao JM, Rosai J. Immunohistochemical detection of epithelial membrane antigen in normal perineurial cells and perineurioma. *Am J Surg Pathol*. 1988;12:678-83. [PMID: 3046395].
6. Hornick JL, Fletcher CD. Soft tissue perineurioma: clinicopathologic analysis of 81 cases including those with atypical histologic features. *Am J Surg Pathol*. 2005;29:845-58. [PMID: 15958848].
7. Folpe AL, Billings SD, McKenney JK, 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;26:1620-6. [PMID: 12459629].
8. Pina AR, Martinez MM, de Almeida OP. Glut-1, best immunohistochemical marker for perineurial cells. *Head Neck Pathol*. 2015;9:104-6. [PMID: 24719203].
9. Emory TS, Scheithauer BW, Hirose T, et al. Intraneural perineurioma. A clonal neoplasm associated with abnormalities of chromosome 22. *Am J Clin Pathol*. 1995;103:696-704. [PMID: 7785653].
10. Macarenco RS, Ellinger F, Oliveira AM. Perineurioma: a distinctive and underrecognized peripheral nerve sheath neoplasm. *Arch Pathol Lab Med*. 2007;131:625-36. [PMID: 17425397].
11. Scheithauer B, Woodruff J, and Erlandson R. Tumors of the Peripheral Nervous System. In: Atlas of Tumor Pathology; 3rd ed. Armed Forces Institute of Pathology; 1999. p. 177-218.
12. Giannini C, Scheithauer BW, Steinberg J, Cosgrove TJ. Intraventricular perineurioma: case report. *Neurosurgery*. 1998;43:1478-81; discussion 81-2. [PMID: 9848865].
13. Balarezo FS, Muller RC, Weiss RG, et al. Soft tissue perineuriomas in children: report of three cases and review of the literature [corrected]. *Pediatr Dev Pathol*. 2003;6:137-41. [PMID: 12545405].
14. Fetsch JF, Miettinen M. Sclerosing perineurioma: a clinicopathologic study of 19 cases of a distinctive soft tissue lesion with a predilection for the fingers and palms of young adults. *Am J Surg Pathol*. 1997;21:1433-42. [PMID: 9414186].
15. Burgues O, Monteagudo C, Noguera R, et al. Cutaneous sclerosing Pacinian-like perineurioma. *Histopathology*. 2001;39:498-502. [PMID: 11737308].
16. Ushigome S, Takakuwa T, Hyuga M, et al. Perineurial cell tumor and the significance of the perineurial cells in neurofibroma. *Acta Pathol Jpn*. 1986;36:973-87. [PMID: 2875597].
17. Diaz-Flores L, Alvarez-Arguelles H, Madrid JF, et al. Perineurial cell tumor (perineurioma) with granular cells. *J Cutan Pathol*. 1997;24:575-9. [PMID: 9404856].
18. Zamecnik M. Perineurioma with adipocytes (lipomatous perineurioma). *Am J Dermatopathol*. 2003;25:171-3; author reply 3-4. [PMID: 12652204].
19. Rank JP, Rostad SW. Perineurioma with ossification: a case report with immunohistochemical and ultrastructural studies. *Arch Pathol Lab Med*. 1998;122:366-70. [PMID: 9648907].
20. Mentzel T, Kutzner H. Reticular and plexiform perineurioma: clinicopathological and immunohistochemical analysis of two cases and review of perineurial neoplasms of skin and soft tissues. *Virchows Arch*. 2005;447:677-82. [PMID: 16133356].
21. Dominguez-Malagon HR, Serrano-Arevalo ML, Maldonado J, et al. Perineurioma versus meningioma. A multi-institutional

immunohistochemical and ultrastructural studY. *Ultrastruct Pathol*. 2021;45:71-7. [PMID: 33320025].
22. Donhuijsen K, Sastry M, Volker B, Leder LD. Mast cell frequency in soft tissue tumors. Relation to type and grade of malignancy. *Pathol Res Pract*. 1992;188:61-6. [PMID: 1594501].
23. Agaimy A, Wuensch PH. Perineurioma of the stomach. A rare spindle cell neoplasm that should be distinguished from gastrointestinal stromal tumor. *Pathol Res Pract*. 2005;201:463-7. [PMID: 16136753].
24. Vargas TJ, Sousa MA, Sampaio AL, et al. Sclerosing perineurioma: case report and literature review. *An Bras Dermatol*. 2009;84:643-9. [PMID: 20191176].
25. 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;16:293-8. [PMID: 12692193].
26. Yamaguchi U, Hasegawa T, Hirose T, et al. Sclerosing perineurioma: a clinicopathological study of five cases and diagnostic utility of immunohistochemical staining for GLUT1. *Virchows Arch*. 2003;443:159-63. [PMID: 12836021].
27. Pitchford CW, Schwartz HS, Atkinson JB, Cates JM. Soft tissue perineurioma in a patient with neurofibromatosis type 2: a tumor not previously associated with the NF2 syndrome. *Am J Surg Pathol*. 2006;30:1624-9. [PMID: 17122521].
28. Schaefer IM, Strobel P, Thiha A, et al. Soft tissue perineurioma and other unusual tumors in a patient with neurofibromatosis type 1. *Int J Clin Exp Pathol*. 2013;6:3003-8. [PMID: 24294391].
29. Khalifa MA, Montgomery EA, Ismiil N, et al. What are the CD34+ cells in benign peripheral nerve sheath tumors? Double immunostaining study of CD34 and S-100 protein. *Am J Clin Pathol*. 2000;114:123-6. [PMID: 10884807].
30. Aiba S, Tabata N, Ishii H, et al. Dermatofibrosarcoma protuberans is a unique fibrohistiocytic tumour expressing CD34. *Br J Dermatol*. 1992;127:79-84. [PMID: 1382538].
31. West KL, Cardona DM, Su Z, et al. Immunohistochemical markers in fibrohistiocytic lesions: factor XIIIa, CD34, S-100 and p75. *Am J Dermatopathol*. 2014;36:414-9. [PMID: 24162384].
32. Kubota R, Nishida H, Kodo Y, et al. A Case of Dendritic Cell Neurofibroma With Pseudorosettes. *Am J Dermatopathol*. 2020;42:604-607. [PMID: 32701696].
33. Tsuzuki T, Ujihira N, Ando T. Usefulness of epithelial membrane antigen (EMA) to discriminate between perineural invasion and perineural indentation in prostatic carcinoma. *Histopathology*. 2005;47:159-65. [PMID: 16045776].