CASE REPORT

Perineuroma of the skin negative for S100 protein but positive for stem cell antigens: A possible stem cell tumor

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ABSTRACT

Perineuroma is a rare tumor originating from perineurium of the peripheral nerve. In contrast to neurofibroma and schwannoma, both of which arise from endoneurium and are immunohistochemically positive for S100 protein, perineuroma is negative for S100 protein; the fact makes the pathologic diagnosis difficult. As is well known, stem cells are highly associated with neuronal and organ developments in human embryos, and some neuronal cells are suspected to be derived from neuronal stem cells. Herein reported a very rare case of subcutaneous perineuroma negative for S100 protein but positive for a number of stem cell antigens; the case suggested that some perineuromas could arise from neuronal stem cells. A 68-year-old woman presented with a skin tumor of 10 mm in diameter in the foot. Physical examination revealed a small movable subcutaneous tumor, and resection was performed. Histologically, the tumor was a well-defined round tumor measuring 0.9 cm × 0.9 cm × 0.9 cm located in the subcutaneous tissue. No capsule was seen. The tumor was composed of hypocellular myxoid, neurid tissues containing small areas of high cellularity where tumor cells resembled neuronal stem cells. Immunohistochemically, the tumor was negative for S100 protein, HMB-45, various cytokeratin (CK), EMA, α-SMA, desmin, p53, and many other antigens. The neuronal stem cell-like cells were positive for various stem cell antigens including NSE, KIT, bcl-2, chromogranin, synaptophysin, PDGFRA, MET, ErbB2, and CD34, as well as for vimentin and Ki-67 antigen (labeling index = 1.5%). Because the tumor was negative for S100 protein but positive for neuroendocrine molecules and neuronal stem cell antigens, the author diagnosed the tumor as perineuroma with stem cell features. Such a perineuroma has not been reported to date. The outcome of the patient was excellent.

Key Words: Perineuroma, S100 protein, Stem cells, Immunohistopochemistry

1. INTRODUCTION

The peripheral nerve system contains secondary motor nerve, first sensory nerve, and the autonomous nerve system composed of sympathetic and parasympathetic neurons. The former two forms are composed of neuron axis, schwann cells, and other supporting cells such as perineurium, endoneurium and epitherium. The autonomous nerve system contains ganglion cells in addition to the supporting cells.

Several kinds of benign peripheral nerve tumors are seen in clinical settings. Almost all of them are schwannoma and neurofibroma. As mentioned above, the peripheral nervous system is composed of endoneurium, epineurium and perineurium.[1] Perineuroma and its related tumors of neurothekeoma and nerve sheath myxoma are categorized as per-
ineural tumors, though the histological features were somewhat different from each other.\(^2\)-\(^8\) The classification and morphology of these three tumors are debatable; Table 1 shows brief characteristics of benign peripheral nerve tumors.

The most important immunopathologic antigen in diagnostic pathology in peripheral nerve system is the S100 protein. It is very sensitive but not specific. Its positive antigenicity is seen in most peripheral nerve tumors, but it is negative in perineuroma (see Table 1). However, S100 protein is not specific to nerve; it is expressed in various cell types including fat, cartilage, melanocytes, macrophages, Langerhan cells, myoepithelial cells, and so on.

**Table 1. List of benign peripheral nerve sheath tumors and their characteristics**

| S100 immunoreaction | Clinicopathologic features |
|----------------------|---------------------------|
| Schwannoma           | +                         | Encapsulated, Antoni A+B, hemosiderin, palisading, vessels |
| Neurofibroma          | +                         | Consisted of schwann and fibrous cells |
| Neurofibromatosis     | +                         | NF1 and NF2, NF gene. Histologically the same as neurofibroma |
| Traumatic neuroma     | +                         | History of trauma. Composed of small nerve tissues |
| Neurothekeoma         | +                         | Nerve sheath origin. Myxoid nerve with intermittent fibrous tissues |
| Nerve sheath myxoma   | +                         | Nerve sheath origin. Histologically very similar to neurothekeoma, but is more myxoid |
| Perineurioma          | −                         | Very similar to neurofibroma but S100 negative |
| Ganglieneuroma        | +                         | Composed of ganglion cells and schwann cells |
| Paraganglioma         | +                         | Also called as pheochromocytoma. Chromaffin cells. S100 positive sustencular cells |

Stem cells play an important role in the embryonic development of nervous systems. In central neural tumors and some peripheral nerve tumors, in particular neurofibromatosis, are derived from neural stem cells.\(^9\),\(^10\) However, there have been no cases of perineuroma, neurothekeoma, and nerve sheath myxoma with stem cell features.

2. **CASE REPORT**

A 68-year-old woman noticed a small skin tumor in the foot, and consulted to our hospital. Physical examination revealed a small subcutaneous tumor in the foot skin or soft tissue. The tumor measured 10 mm × 11 mm × 11 mm and showed tenderness. The tumor was movable by palpation. No lymph node swelling was noted, and the skin overlying the tumor was almost normal though it was mildly reddish. The routine blood test was almost within normal ranges. A resection of the tumor was performed. Histologically, the tumor was located in the subcutaneous tissue (see Figure 1A). The tumor was a well-defined round tumor measuring 0.9 cm × 0.9 cm × 0.9 cm (see Figure 1A). No capsule was seen. The tumor was composed of hypocellular myxoid, and neuroid tissues (see Figure 1B) containing small cellular areas where the tumor cells resembled neural stem cells (see Figure 1C). No atypical features or mitotic figures were seen. No invasive features were recognized.

Immunohistochemically, the tumor was negative for S100 protein, cytokeratin (CK) 14, CK AE1/3, CK CAM5.2, epithelial membrane antigen (EMA), \(\alpha\)-smooth muscle actin (ASMA), melanosome antigen human melanoma black 45 (HMB45), desmin, cancer carbohydrate antigen 19-9 (CA19-9), protein (P) p53, cluster differentiation (CD) CD68, p63, CD45, CD3, CD20, CD10, myoglobin, cyclin-dependent kinase-4 (CDK4), mouse double minute 2 (MDM2) homolog, mucin core protein (MUC) MUC1, MUC2, MUC5AC, and MUC6. The cellular neural stem cell-like cells were positive for neuron-specific enolase (NSE) (see Figure 2A), KIT or CD117 (see Figure 2B), B-cell lymphoma 2 (bcl-2) (see Figure 2C), chromogranin, synaptophysin (see Figure 2D), platelet-derived growth factor receptor-alpha (PDGFR\(\alpha\)) (see Figure 2E), met gene (MET, also known as hepatocyte growth factor receptor) (see Figure 2F), neu gene (ERBB gene, erb-h2 gene, erb2 gene (ErbB2, also known as human epidermal growth factor receptor 2 and HER2/neu), CD34, vimentin, and Ki-67 antigen (clone MIB1) (labeling index = 1.5\%). Because neuroendocrine antigens and antigens of neural stem cells were positive but S100 protein was negative, the author diagnosed the tumor as perineuroma with stem cell features. Such a perineuroma with stem cell features has not been reported. The outcome of the patient was excellent.

3. **DISCUSSION**

The present tumor histologically showed benign neuroid features. The tumor was small and located in the subcutaneous tissue. The tumor was not encapsulated, but it was well
demarcated from the surrounding tissue. The hematoxylin and eosin histologies suggests a schwannoma, neurofibroma, nerve sheath myxoma, neurothekeoma, or perineuroma. An immunohistochemical study was done to determine the diagnosis and to evaluate the stem cell features. Interestingly, it showed that the tumor was negative for S100 protein. Thus, schwannoma and neurofibroma, both of which are almost always positive for S100 protein were denied by histology as well as by immunohistochemistry.

![Figure 1. Histology of the tumor](http://crcp.sciedupress.com)

**A:** Very low power view. The tumor is located in the submucosa and measuring 0.9 cm × 0.9 cm × 0.9 cm. The tumor is well defined but has no capsule. HE, ×20. **B:** Medium power view. The tumor is composed of myxoid, neuroid matrix. No atypical features are seen. HE, ×100. **C:** High power view of the relatively cellular areas. These area are less than 5% in areas in the tumor. Spindle cells and stem cell-like cells are seen. No atypical features are seen. HE, ×200

The Immunohistochemical study showed that the neural stem cells-like areas with high cellular density showed neuroendocrine features (NCAM, NSE, chromogranin and synaptophysin). These findings suggest that the tumor is of perineurium origin. Thus, perineuroma, neurothekeoma, and nerve sheath myxoma were probable; the latter two can be negative for S100. The separation and classification of these three tumors are debatable. Because, the myxoid changes seen in nerve sheath myxoma were not prominent and characteristic nested pattern present in neurothekeoma was absent in the present case, the author denied neurothekeoma and nerve sheath myxoma both of which were frequently S100-positive, and diagnosed this tumor as perineuroma.

The present perineuroma is unique, because many stem cell antigens were expressed in the neural stem cells-like areas showing a high cellularity. That is, the neural stem cells-like areas were positive for many stem cell antigens, i.e. KIT, NCAM, NSE, synaptophysin, chromogranin, bcl-2, PDGFRA, MET, ErbB2, and CD34.[11–27] These findings strongly suggest the close association between the present tumor and neural stem cells.[11–27] It can be plausible that the present tumor arose from neural stem cells. That is, there is a
possibility that the present tumor is a kind of stem cell tumor. In embryonic development of humans, almost all nerve systems are made by embryonic stem cells. Some nerve tumors of soft tissue are thought to be derived from stem cells.\textsuperscript{[9, 10]} These findings suggest that the present perineuroma were derived from neural stem cells.

In the present case, KIT, PDGFRA, MET, and ErbB2 were expressed in the tumor. These findings suggest that stem cell factor/KIT, platelet-derived growth factor-alpha/PDGFR\textalpha, hepatocyte growth factor/MET, and epidermal growth factor/ErbB2 signaling pathways play an important role in the tumorigenesis and tumor growth in the present perineuroma.\textsuperscript{[11–27]}

In the present case, CK14 (a stem cell antigen) was negative, suggesting that all stem cell markers are not expressed in the present possible stem cell tumors. The present tumor showed negative expression of CK AE1/3, CK CAM5.2 and EMA, indicating that the present tumor is not an epithelial tumor. The positive expression of vimentin indicates that the present tumor is a mesenchymal tumor. The negative expressions of ASMA, desmin, and myoglobin suggest that the present tumor is not myogenic tumor. The negative expression of S100 and HMB45 suggest that the present tumor is not melanocytic tumor or nevi. The negative expression of p53 suggests no p53 mutations and benign nature of the present tumor. The negative p63 suggests that the tumor is not epithelial carcinoma and not myoepithelial carcinoma. The negative expressions of CD68, CD45, CD3, CD20, and CD10 indicate that the present tumor is not a leukocytic neoplasm including lymphoma and granulocytic sarcoma. The negative CDK4 and MDM2 imply that the present tumor is not atypical lipomatous tumor (well differentiated liposarcoma). The negative MUC1, MUC2, MUC5AC, and MUC6 showed the mucins of the myxoid areas do not have MUC1 and MUC2, MUC5AC and MUC6 mucins backbone proteins.

4. CONCLUSIONS

The author herein presented a very rare case of perineuroma in the subcutaneous tissue of the foot. The tumor was characterized by negative S100 and positive stem cell markers. It was strongly suggested that the present perineuroma might have arisen from neuronal stem cells.

CONFLICTS OF INTEREST DISCLOSURE

The author declares no conflicts of interest.
REFERENCES

[1] Pi-a-Oviedo S, Ortiz-Hidalgo C. The normal and neoplastic perineurium: a review. Adv Anat Pathol. 2008; 15: 147-64. PMid: 18434767. http://dx.doi.org/10.1097/PAP.0b013e3181f8519

[2] 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. http://dx.doi.org/10.1097/01.PAS.0000155166.86409.d2

[3] Pitchford CW, Schwartz HS, Atkinson JB, et al. 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. http://dx.doi.org/10.1097/01.PAS.0000213340.70882.d4

[4] Zamecnik M, Chlumska A. Perineurioma versus fibroblastic polyph of the colon. Am J Surg Pathol. 2006; 30: 1337-9. PMid: 17001168. http://dx.doi.org/10.1097/01.PAS.0000155140.87219.2c

[5] Hornick JL, Bundock EA, Fletcher CD. Hybrid schwannoma/perineurioma: clinicopathologic analysis of 42 distinctive benign nerve sheath tumors. Am J Surg Pathol. 2009; 33: 1554-61. PMid: 19623031. http://dx.doi.org/10.1097/PAS.0b013e3181acc6ce

[6] Hornick JL, Fletcher CD. Intestinal perineurioma: clinicopathologic definition of a new anatomic subset in a series of 10 cases. Am J Surg Pathol. 2005; 29: 895-65. http://dx.doi.org/10.1097/01.PAS.0000154130.70882.4d

[7] Fetsch JF, Laskin WB, Hallman JR, et al. Neurothekeoma: an analysis of 178 tumors with detailed immunohistochemical data and long-term patient follow-up information. Am J Surg Pathol. 2007; 31: 1103-14. PMid: 17592278. http://dx.doi.org/10.1097/PAS.0b013e31802d496a

[8] Fetsch JF, Laskin WB, Miettinen M. Nerve sheath myxoma: a clinicopathologic and immunohistochemical analysis of 57 morphologically distinctive, S-100 protein- and GFAP-positive, myxoid peripheral nerve sheath tumors with a predilection for the extremities and a high local recurrence rate. Am J Surg Pathol. 2005; 29: 1615-24. PMid: 16327434. http://dx.doi.org/10.1097/01.PAS.0000170025.87476.a4

[9] Pongpudpunth M, Bhawan J, Al-Natour SH, et al. Nestin-positive stem cells in neurofibromas from patients with neurofibromatosis type 1-tumorigenic or incidental? Am J Dermatopathol. 2010; 32: 574-7. PMid: 20520523. http://dx.doi.org/10.1097/DAD.0b013e3181b0d7c

[10] Morris ZS, McClatchey AI. The neurofibroma cell of origin: SKPs expand the playing field. Cell Stem Cell. 2009; 4: 371-2. PMid: 19427284. http://dx.doi.org/10.1016/j.stem.2009.04.010

[11] Naldini L, Weidner KM, Vigna E, et al. Scatter factor and hepatocyte growth factor are indistinguishable ligands for the MET receptor. EMBO J. 1991; 10: 2867-78. PMid: 1655405.

[12] Hoch RV, Soriano P. Roles of PGDR in animal development. Development. 2003; 130: 4769-84. PMid: 12952899. http://dx.doi.org/10.1242/dev.00721

[13] Roskams T. Liver stem cells and their implication in hepatocellular and cholangiocarcinoma. Oncogene. 2006; 25: 3818-22. PMid: 16799623. http://dx.doi.org/10.1038/sj.onc.1209558

[14] Allison MR. Liver stem cells: implication for hepatocarcinogenesis. Stem cell Rev. 2005; 1: 253-60. http://dx.doi.org/10.1385/SCR:1:3:253

[15] Strain AJ, Crosby HA. Hepatic stem cells. Gut. 2000; 46: 743-50. http://dx.doi.org/10.1136/gut.46.6.743

[16] Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumor. Science. 1998; 279: 877-80. PMid: 9438854. http://dx.doi.org/10.1126/science.279.5350.877

[17] Cassiman D, Denef C, Desmet VJ, et al. Human and rat hepatic stellate cells express neurotrophins and neurotrophin receptors. Hepatology. 2001; 33: 148-58. PMid: 11124831. http://dx.doi.org/10.1053/jhep.2001.20793

[18] Cassiman D, Libbrecht L, Sinelli N, et al. The vagal nerve stimulates activation of the hepatic progenitor cell compartment via muscarinic acetylcholine receptor 3. Am J Pathol. 2002; 161: 521-30. http://dx.doi.org/10.1016/S0002-9440(04)64620-8

[19] Sirica AE. Role of ErbB2 family receptor tyrosine kinase in intrahepatic cholangiocarcinoma. World J Gastroenterol. 2008; 14: 7033-58. PMid: 19084911. http://dx.doi.org/10.3748/wjg.14.7033

[20] Fabris L, Strazzabosco M, Crosby HA, et al. Characterization and isolation of ductular cells expressing neural cell adhesion molecule and cld-2 from primary cholangiopathy and ductal plate malformations. Am J Pathol. 2000; 156: 1599-12. http://dx.doi.org/10.1016/S0002-9440(04)65032-8

[21] Cassiman D, Sinelli N, Bockx I, et al. Human hepatic progenitor cells express vasoactive intestinal peptide receptor type 2 and receive nerve endings. Liver Int. 2007; 27: 323-8. PMid: 17355452. http://dx.doi.org/10.1111/j.1478-3231.2006.01427.x

[22] Oben JA, Roskams T, Yang S, et al. Sympathetic nervous system inhibition increases hepatic progenitors and reduces liver injury. Hepatology. 2003; 38: 664-73. http://dx.doi.org/10.1053/jhep.2003.05371

[23] Oben JA, Roskams T, Sinelli N, et al. Hepatic fibrogenesis requires sympathetic neurotransmitters. Gut. 2004; 53: 438-45. PMid: 14960531. http://dx.doi.org/10.1136/gut.2003.026658

[24] Ueno T, Tanikawa K. Intralobular innervation and lipocyte contractility in the liver. Nutrition. 1996; 13: 141-8. http://dx.doi.org/10.1086/208999-9007(96)00389-9

[25] Ueno T, Bioulac-Sage P, Balabaud C, et al. Innervation of the sinusoidal wall: regulation of the sinusoidal diameter. Anat Rec. 2004; 280A: 868-73. PMid: 15382014. http://dx.doi.org/10.1002/ar.a.20092

[26] Bioulac-Sage P, Lafon ME, Saric J, et al. Nerves and perisinusoidal cells in human liver. J Hepatol. 1990; 10: 280A: 868-73. PMid: 15382014. http://dx.doi.org/10.1002/ar.a.20092

[27] Cardinale V, Wang Y, Carpino G, et al. Mucin-producing cholangiocarcinoma might derive from biliary tree stem/progenitor cells located in peribiliary glands. Hepatology. 2012; 55: 2041-2. PMid: 22262336. http://dx.doi.org/10.1002/hep.25587