Hybrid peripheral nerve sheath tumor

Case report

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In recent literature, there have been case reports of an extremely rare entity characterized by hybrid peripheral nerve tumors consisting of elements of neurofibroma, schwannoma, and/or perineurioma. The authors present a unique case of a patient with multiple painful hybrid tumors with negative genetic testing for neurofibromatosis Type 1 and no clinical evidence of neurofibromatosis Type 2 or schwannomatosis.

A 28-year-old woman presented with tentatively diagnosed schwannomatosis. She had painful bilateral retromastoid scalp tumors as well as multiple other painful tumors in the distribution of the saphenous, femoral, and sciatic nerves. Her family history was significant for a paternal grandfather with a solitary schwannoma. The patient underwent multiple surgical procedures for tumor resection, including tumors in the regions of the retromastoid scalp, bilateral sciatic nerves, left femoral nerve, and left axilla. These tumors were examined and evaluated histologically. Within the tumors, components of both neurofibromas and schwannomas were found, even though these 2 peripheral nerve sheath tumors have been long considered to be distinct entities. This case report suggests a distinct syndrome that has not previously been appreciated.

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KEY WORDS • neurofibroma • schwannoma • hybrid tumor • peripheral nerve sheath tumor

NEUROFIBROMAS and schwannomas are the 2 most common benign PNSTs. Schwann cells are the cells of origin for both of these tumors.6,19 Neurofibromas grossly may be fusiform, globular, plexiform, or diffuse and comprise a variety of cells, including Schwann cells, perineurial-like cells, fibroblasts, and transitional cells. In contrast, schwannomas are globular or plexiform nerve sheath tumors composed entirely of Schwann cells.2,23 Intraneural perineuriomas are rare nerve sheath tumors composed of well-differentiated perineurial cells exhibiting immunoreactivity for EMA.2,11,23 An extremely rare entity of a hybrid neurofibroma and schwannoma has been reported, suggesting a closer relationship between these lesions than had been previously understood.5 We describe the case of a 28-year-old woman with multiple painful benign nerve sheath tumors that had features of both neurofibromas and schwannomas. The patient tested negative for germline mutations, and her tumor tested negative for somatic mutations in NFI. Clinically, the patient did not have any features of NF2, and histologically the tumors were not consistent with schwannomatosis.12,13

Case Report

Presentation and Examination. This 28-year-old woman presented with a 15-year history of tentatively diagnosed NF1 or schwannomatosis. She presented with numerous soft-tissue masses in a widespread distribution, including the scalp, legs, arms, and pelvic regions most symptomatically. Bilateral retromastoid scalp region masses prevented her from sleeping. She reported local tenderness and distal neuropathic pain in the distributions of bilateral saphenous nerves, bilateral sciatic nerves, left femoral nerve, and left mons pubis.

The patient’s family history was only significant for a paternal grandfather with one isolated schwannoma. She was first treated at another institution in 2001 and was told

Abbreviations used in this paper: EMA = epithelial membrane antigen; NF1 = neurofibromatosis Type 1; NF2 = neurofibromatosis Type 2; PNST = peripheral nerve sheath tumor.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
at various times that she had NF1 or schwannomatosis. In 2002, she had a left middle finger and right breast tumor excision. In 2005 she underwent a left proximal sciatic, right femoral, and distal medial thigh tumor excision. She had undergone resection of several tumors prior to her presentation at our institution, starting in 2008. On physical examination, she had no stigmata of NF1 or NF2, including no dermatological features of either disease. She did not have any other clinical features of NF1 or NF2, such as acoustic neuromas or ophthalmological abnormalities seen in either disease. Prior to surgery, she was neurologically intact, although pain limited strength testing in her left hip flexor in particular.

The MRI and CT scans revealed multiple nerve sheath tumors in the intercostal nerves and in the retroperitoneum and pelvis (especially in the right psoas region); pulmonary nodules (with no evidence of pulmonary fibrosis); bilateral involvement of lumbar/sacral nerve roots and sciatic and femoral nerves; and tumors in the proximal calves, upper extremity, and chest (Fig. 1). The homogeneous bright signal seen on the STIR sequences in this case is a common appearance of schwannomas and neurofibromatosis, although it is unusual for solitary neurofibromas. Magnetic resonance imaging findings of the brain and spine were negative for vestibular schwannomas, ependymomas, gliomas, or meningiomas.

**Operation.** The patient’s first surgical procedure at the University of Pennsylvania in 2008 involved the removal of bilateral painful retromastoid scalp lesions that interfered with her sleep. Additionally, because of the pain in the distribution of her right sciatic nerve, a palpable mass was resected from the proximal right posterior thigh, and exploration of the previously resected right saphenous nerve mass was performed, which revealed a painful scar neuroma. The next surgical procedure in 2008 involved removal of two 3-cm tumors from her left posterior thigh and medial buttock in the distribution of the sciatic nerve. In 2009, she underwent removal of a left mons pubis lesion and a large left femoral nerve sheath tumor. Postoperatively, she was stable during her neurological examination, except that she was transiently slightly weaker in her left hip flexor but was able to bear weight. Over the next few months, she made an excellent recovery with normal strength and sensation.

**Postoperative Course.** The patient’s most recent surgical procedure in 2011 involved the removal of tumors from the left infraclavicular brachial plexus, the left breast, and the right medial thigh. All of the lesions were firm, well-encapsulated masses that arose from the nerve with one small fascicle entering and exiting at the poles of the tumor. Gross-total resection was performed in each case, with the assistance of neural monitoring.

**Genetic Testing.** Clinical genetic testing for mutations in NF1 was done at the University of Alabama (L. Messian laboratory). Initial genetic testing of the patient’s white blood cells (germline) was negative, with sequencing of all coding exons, copy number analysis using MLPA (Multiplex Ligand-dependent Probe Amplification), microsatellite marker analysis, and RNA studies for deep intronic splice mutations. Subsequently, resected tumor was sent to the Messian laboratory so that Schwann cells could be grown and tested to identify a mutation in NF1. Again, the analysis, as above, was done, and no mutation was identified in NF1 in the Schwann cells.

**Histopathological Examination.** Gross examination of the resected tumor specimens from all operations performed at the University of Pennsylvania revealed an encapsulated, bilobed tan-yellow mass with attached proximal and distal nerve fascicles. At the University of Pennsylvania, the patient had 15 tumors resected, which were all reviewed by a neuropathologist (T.M.C.). These 15 independent tumors, which were resected over a period of several years and were removed from various anatomical locations, as described above, were indistinguishable from each other. All of the tumors exhibited the same histology and immunohistochemical staining results. Pathological specimen reports from an outside hospital were also reviewed by a neuropathologist (T.M.C.). The tumors resected at the outside institution were reported as having the same histology and immunohistochemical staining patterns as the tumors analyzed at our institution. Upon sectioning, the tumor exhibited a glistening, homogeneous tan-white cut surface. Microscopically, the specimens were morphologically consistent with a neurofibroma (Fig. 2a). The sections showed a tumor comprising small spindle-shaped cells with minimal cytoplasm and wavy to oval nuclei. These cells were embedded in a myxoid stroma with varying collagen deposition, including areas with thick bundles exhibiting the classic “shredded carrot” appearance (Fig. 2b). Within the neu-

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**Fig. 1.** a: Coronal STIR sequence through the upper chest and left upper arm demonstrating the presence of high-signal masses involving multiple intercostal nerves and the proximal median nerve. b: Coronal STIR sequence through the pelvis and thighs demonstrating diffuse involvement of bilateral sacral and sciatic nerves by high-signal nerve sheath tumors. c: Axial STIR sequence through the pelvis demonstrating multiple high-signal masses involving the sacral nerves. d: Axial, fat-saturated T1-weighted MRI sequence obtained through the same level as in panel c after the injection of Gd contrast agent. Note patterns of both peripheral enhancement and lack of enhancement of the masses, reflecting relative avascularity of the nonenhancing regions.
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atrofibromas of all specimens examined, there were distinct nodules or tumorlets ranging in size from 500 μm to 3 mm that were morphologically consistent with a schwannoma. These tumors were encompassed by the neu- rofibromatous elements with abrupt transition from neu- rofibroma to schwannoma (Fig. 2c). The schwannomas comprised spindle cells with hyperchromatic, elongated nuclei organized in compact whorls (the Antoni Type A pattern), admixed with focal areas that were more loosely organized with variable lipidization (the Antoni Type B pattern) (Fig. 2d). Adjacent to the schwannoma tumorlets were numerous onion bulb–type formations, characteristic of hypertrophic neuropathy (Fig. 2e and f). These hybrid features were present in all specimens examined.

Immunohistochemical stains for S100 protein, EMA, CD34, phosphorylated neurofilament (NF-TA51), and INI-1 were performed on representative sections of tumor from multiple resection specimens across multiple anatomical locations. The immunohistochemical profile of the hybrid lesions was characteristic of the individual components. Neurofibromas comprise a mixture of the following 3 cell types: S100-positive Schwann cells, EMA/Grail-1-positive perineurial cells, and CD34-positive fibroblast-like support cells. In contrast, schwannomas are composed entirely of Schwann cells. The S100 stain highlighted the spindle-shaped Schwann cells in both the neurofibroma and schwannoma tumorlets (Fig. 3a and b). In addition, the onion bulb formations were entirely S100 positive (Fig. 3c). The EMA stain only highlighted scattered perineural cells in the tumor and residual perineurium (Fig. 3d). Immunoreactivity for CD34 was limited to scattered fibroblast-like cells and vasculature (Fig. 3e). Moreover, schwannoma tumorlets and the onion bulb structures were negative for EMA and CD34. Intraneural perineuriomas display similar onion bulb–type formations, but they are composed of EMA-positive perineurial cells. In contrast, the onion bulbs associated with hypertrophic neuropathy are composed of concentric layers of Schwann cells, characterized by S100-positive and EMA-negative immunoreactivity, as in the present case. The NF-TA51 highlighted scattered entrapped axons in all neurofibromatous areas, but not in the schwannoma tumorlets (Fig. 3f). Lastly, the INI-1 stain showed strong nuclear reactivity in the tumor cells (Fig. 3g). INI-1 is a protein encoded by the SMARCbl gene in which mutations have been shown to cause schwannomatosis. INI-1 expression within the nucleus is totally or partially lost in schwannomatosis.23

Discussion

Peripheral nerve sheath tumors include neurofibromas, schwannomas, and perineuriomas, all of which are generally considered discrete entities.2,11,23 In recent years, there have been 66 reported cases of hybrid PNSTs, which include neurofibroma/perineurioma, schwannoma/perineurioma, and neurofibroma/schwannoma hybrid tumors. In the reported cases the tumor locations are almost exclusively in the digits or extremities.3,4,9–11,14,15,20,24 However, atypical sites such as the colon have been described.5 Hornick et al.5 reported 42 cases of schwannoma/perineurioma hybrid PNSTs. The largest series of a neurofibroma/schwannoma hybrid PNST was discussed by Feany et al.5 Of 9 patients in their case series, 5 also had plexiform neurofibromas, which they considered pathognomonic of NF1; however, none of those 5 patients met clinical diagnostic criteria for NF1. One patient had a nonplexiform neurofibroma and a clinical diagnosis of NF1. The 4 remaining patients had no evidence of NF1; thus, the authors demonstrated that hybrid tumors were not confined to patients with NF1. There also has been a report of a large schwannoma and a plexiform neurofibroma arising from the same anatomical region.21 Unlike the present case, the described hybrid tumors tend to be solitary in nature, and in the dermis and subcutis.

Neurofibromatosis Type 1 is the most common of the inherited genetic disorders that give rise to PNSTs.12 In this disorder is a result of a germline mutation in the NF1 gene located on chromosome 17, encoding for the protein neurofibromin.27 Neurofibromatosis Type 1 is clinically diagnosed by having 2 of the following 7 diagnostic criteria: café-au-lait macules, neurofibromas, axillary freckling, optic nerve glioma, Lisch nodules, skeletal dysplasia, and having a first-degree relative with NF1. The clinical criteria used for the diagnosis of NF1 are widely accepted and practiced.
However, there are 2 major subtypes of NF1: segmental disease and “spinal neurofibromatosis.” Segmental NF1 is caused by mosaicism for the NF1 mutation, causing NF1 in only one “segment” of the body. Generally, segmental NF1 is recognized by visualizing the dermatological features in only one part of the body, or by having a group of neurofibromas in only one location. Spinal neurofibromatosis is a variant of NF1, in which patients have very few dermatological features and multiple bilateral spinal neurofibromas. 

Patients with this disease have mutations in NF1 but are more likely to have missense or splice mutations. Neurofibromatosis Type 2 occurs less frequently than NF1 and is associated with a variety of tumors, especially schwannomas, meningiomas, and ependymomas. The NF2 gene is located on chromosome 22 and encodes the protein merlin. The hallmark of NF2 is the development of multiple schwannomas, with the pathognomonic tumor vestibular schwannoma. Schwannomatosis should be considered after NF1 and NF2 have been excluded. Many reports in the literature have discussed the diagnostic criteria for schwannomatosis, and cases are currently categorized as definite, possible, and segmental schwannomatosis. Inherited schwannomatosis was found to be associated with a germline mutation in the SMARCB1/INI1 gene. However, mutations in INI1 only account for a minority of familial cases and an even smaller percentage of sporadic disease. Patients should not have evidence of vestibular tumor(s) on high-quality MRI and also cannot have a known constitutional NF2 mutation. The definition of “possible” schwannomatosis is radiographic evidence of a nonvestibular schwannoma plus a first-degree relative meeting the criteria for definite schwannomatosis. As discussed in detail below, the patient in this report did not have a syndrome consistent with NF1, NF2, or schwannomatosis.

The present case is that of a patient with multiple, bilateral painful tumors exhibiting hybrid features of both neurofibromas and schwannomas. The striking pathological finding in this case is that of hybrid neurofibromas with distinct schwannoma nodules or tumorlets and associated onion bulb formations typical of hypertrophic neuropathy. These morphological features are present in all resected specimens from multiple anatomical locations, including the scalp, the proximal right medial and posterior thigh, left posterior thigh, left mons pubis, left femoral nerve, left infraclavicular brachial plexus, and left breast. Hybrid tumors with schwannoma-like tumorlets and onion bulb–like arrangements are rare and are usually associated with plexiform neurofibromas or solitary neurofibromas in patients with known NF1 mutations or stigmata thereof. In the case described here, the nerve sheath tumors did not exhibit a plexiform configuration or correspond to intraneural lesions. Mosaicism for NF1 (also called segmental NF1) or spinal NF1 cannot be diagnosed in this patient. She does not have any nontumor findings associated with NF1 (for example, café-au-lait macules), and her tumors are dispersed widely throughout her body and involved all extremities and her head, neck, abdomen, and pelvis. Germline and somatic genetic testing of the patient’s white blood cells and tumor tissue, respectively, were screened for mutations, rearrangements, and deep intronic mutations in NF1. Moreover, the patient has no clinical evidence of NF2, and the histological features of the tumors are not consistent with schwannomas. She also does not meet the clinical criteria defined for schwannomatosis. Furthermore, it is important to...

Fig. 3. Immunohistochemical profile of the hybrid tumors. a–c: S100 staining of the neurofibroma (a), schwannoma tumorlet (b), and onion bulb formations (c). d: EMA staining is confined to the perineurium (arrow). Note the negative EMA staining in the onion bulbs (asterisk). e: CD34 staining highlighting stromal support cells and scattered vasculature. f: Neurofilament stain (NF-TA51) highlighting sparse encompassed axonal processes. g: INI-1 nuclear staining is preserved in the tumor cells, including the schwannoma tumorlets depicted here. Bar = 100 μm.
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differentiate this patient’s tumors from schwannomatosis. Mosaic pattern of INI-1 staining loss has been reported in the majority of patients with NF2 and schwannomatosis; however, our patient’s tumors were composed largely of neurofibromas and the tumor cells exhibit strong nuclear staining for INI-1.

The collective clinical, radiological, and pathological findings reveal a novel presentation of multiple hybrid nerve sheath tumors. The development of the hybrid tumors, with conserved morphological features, in multiple locations at an early age is strongly suggestive of an underlying germline mutation, which we have not detected using current methods. This case likely represents a previously uncharacterized syndrome. Unique individuals similar to the one described herein represent an opportunity for the identification of novel susceptibility genes associated with hybrid nerve sheath tumors. With the advent of next-generation sequencing, such individuals provide an opportunity for identification of novel genes associated with nerve sheath tumors.

Disclosure
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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