Recurrent Knee Pain in an Athletic Adult: Multiple Schwannomas Secondary to Schwannomatosis. A Case Report

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Abstract

Schwannomatosis has been used to describe patients with multiple nonvestibular schwannomas with no associated features of neurofibromatosis type 2. In our case, a 28-year-old athletic man underwent a right knee excisional biopsy for multifocal, benign schwannomatosis. After being asymptomatic for 4 years postresection, he returned to our musculoskeletal oncology service. Imaging studies revealed local recurrence identical to his initial presentation. Excisional biopsy of discrete masses was performed and histologic examination revealed recurrent benign schwannomatosis. To our knowledge, this is the second reported case of recurrent benign schwannomatosis. We review schwannomatosis, including its etiology, radiographic features, and relationship to neurofibromatosis.

A 28-year-old athletic man was referred to our musculoskeletal oncology service after reporting right knee discomfort mainly on exertional activities that progressed to persistent pain and numbness on the medial aspect of his right thigh and knee over a period of a few months. Imaging studies (Figures 1, 2) and eventual surgical wide excision of 4 palpable, discrete, medial knee masses (1 superficial, 2 posteromedial located at the superior pole of the patella, and 1 located in the deep fascia) was performed. Histology revealed benign multifocal schwannomatosis. After surgical excision, the patient's pain was completely resolved.

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Four years later, the patient returned owing to recurrent symptoms of pain over discrete areas of the right medial knee. The patient denied any trauma and reported no history of constitutional symptoms, such as fever, chills, or weight loss. The patient also denied any medical- or family-associated history of cancer. The patient provided informed consent for print and electronic publication of this case report.

Physical examination revealed tenderness over the medial aspect of his distal right thigh as well as recurrent tenderness and numbness along the medial knee. A positive Tinel's sign was present, along with evidence of sensory loss in the distribution of the saphenous nerve. No signs of skin changes or lymphadenopathy were present. Laboratory tests, including complete blood count and serum chemistries, revealed levels within normal limits.

Imaging studies, including plain radiographs and a computed tomography (CT) scan, were unremarkable. Magnetic resonance imaging (MRI) (Figures 3, 4) revealed 3 discrete, recurrent masses in the following areas: adjacent to the right posteromedial femoral condyle, approximately 12 cm proximal to the joint line of

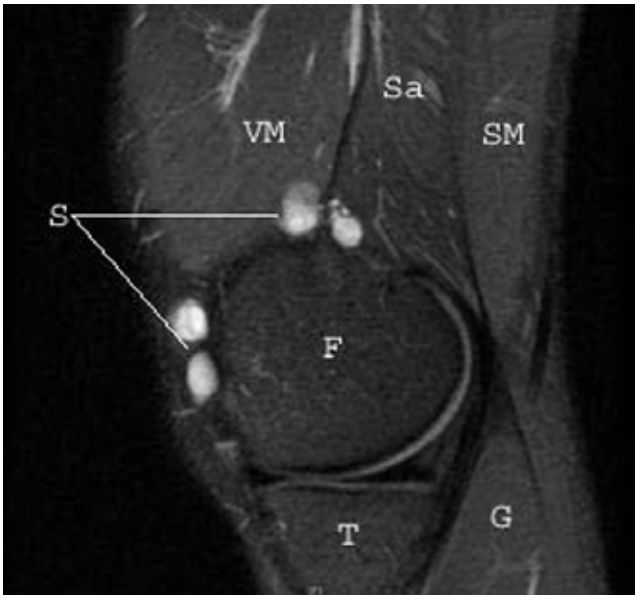

Figure 1. Sagittal T_2-weighted MRI from presentation 4 years earlier, showing 2 lesions at the superior pole of the patella and 2 lesions located in the deep fascia. Abbreviations: F, femur; G, gastrocnemius; MRI, magnetic resonance image; S, schwannoma; Sa, sartorius; SM, semimembranosus; T, tibia; VM, vastus medialis.

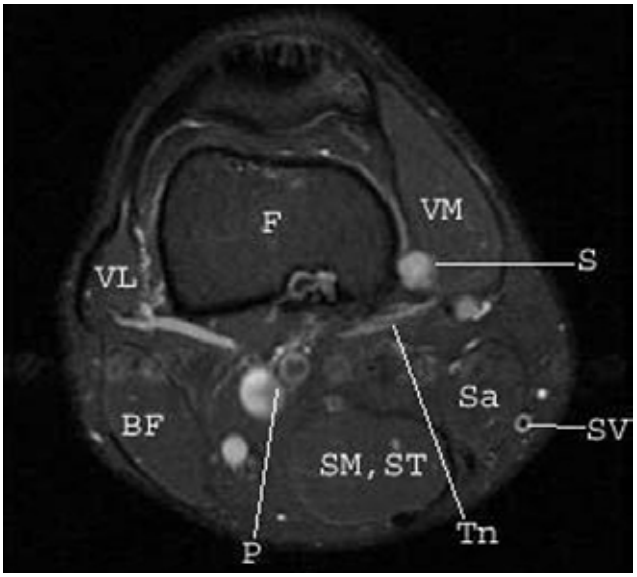

Figure 2. Axial T_2-weighted MRI from earlier presentation showing 2 of the larger lesions located in the posterior medial deep fascia. Abbreviations: BF, biceps femoris; F, femur; MRI, magnetic resonance image; P, popliteal artery and vein; S, schwannoma; Sa, sartorious; SM, semimembranosus; ST, semitendinosus; SV, saphenous vein; Tn, articular branch tibial nerve; VL, vastus lateralis; VM, vastus medialis.

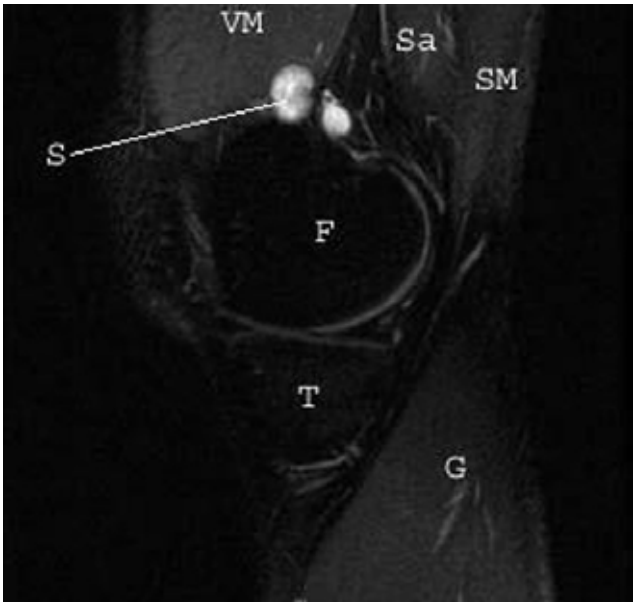

Figure 3. Sagittal T_2-weighted MRI from most recent presentation showing local recurrence of the posterior medial deep fascia lesions. Abbreviations: F, femur; G, gastrocnemius; MRI, magnetic resonance image; S, schwannoma; Sa, sartorius; SM, semimembranosus; T, tibia; VM, vastus medialis.

the right knee, and approximately 20 cm proximal to the right medial femoral flare.

Given the patient's history, physical examination findings, and imaging studies, the expected diagnosis was recurrent schwannomatosis. An excisional biopsy was planned and performed. All of the round-to-oval tumors were invested with epineural tissue.

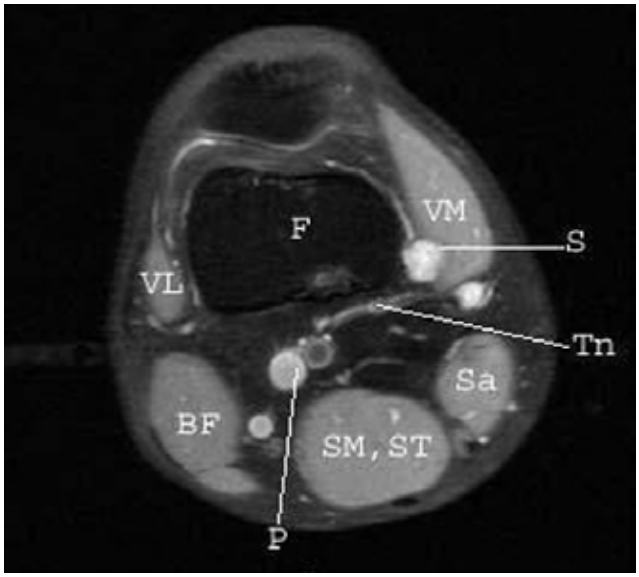

Figure 4. Axial T_2-weighted MRI from most recent presentation showing local recurrence of the posterior medial deep fascia lesions. Abbreviations: BF, biceps femoris; F, femur; MRI, magnetic resonance image; P, popliteal artery and vein; S, schwannoma; Sa, sartorious; SM, semimembranosus; ST, semitendinosus; SV, saphenous vein; Tn, articular branch tibial nerve; VL, vastus lateralis; VM, vastus medialis.

The surgically removed specimens were confirmed histologically to be benign schwannomatosis with areas of Antoni A and Antoni B tissue. Immunohistochemical staining revealed that most tumor cells reacted strongly for S-100 protein. The patient has had no further complications or relapses with over a year of clinical follow-up to monitor for disease recurrence.

Discussion

Treatment of peripheral nerve tumors is reserved for lesions that are malignant or cause neurologic dysfunction, pain, compressive symptomatology, or cosmetic concern. The prognosis of benign peripheral nerve tumors is excellent, with a recurrence rate of 5% or less after successful surgery. A schwannoma is a type of benign nerve sheath tumor that most commonly occurs solitarily in otherwise healthy individuals. Recently, if multiple nonvestibular nerve schwannomas develop in an individual synchronously or metachronously, a defined form of neurofibromatosis, called schwannomatosis or neurilemmomatosis, can be diagnosed.[1,2] Diagnosis of schwannomatosis is dependent on finding multiple schwannomas in the absence of the bilateral vestibular schwannomas (BVS) characteristic of neurofibromatosis type 2 (NF-2).[3] It is possible that a patient who presents with multiple nonvestibular schwannomas could later develop bilateral acoustic neuromas, thus meriting a diagnosis of NF-2.[3] In addition, a patient with a unilateral vestibular schwannoma with concurrent nonvestibular schwannomas would be classified

as having schwannomatosis unless bilateral acoustic neuromas developed.

The authors note a paucity of reported cases of multifocal schwannomatosis in the literature when compared with cases of single nerve sheath lesions. In fact, of patients presenting with schwannoma, 3% to 4% are found to have multiple lesions.[4] In 1 particular retrospective study, Huang and colleagues revisited 131 consecutive patients treated for schwannoma and concluded that only 6 patients presented with multiple schwannomas resulting in a diagnosis of schwannomatosis.[5] Furthermore, none of the 131 patients suffered a local recurrence.

To date, there have been only 2 reported instances of benign recurrent schwannoma; 1 of which initially presented as multifocal schwannoma or schwannomatosis. Isenberg and colleagues first reported a case of multiple concurrent and recurrent benign schwannomas of the upper extremity.[6] The other known case of recurrent schwannoma was reported by Yammamoto. In this case report, the authors describe a middle-aged woman who had a successful excisional biopsy of a single benign schwannoma originating from the sciatic nerve in her left popliteal region that recurred as schwannomatosis a decade later.[1] In both cases, the patients did not fit the criteria for neurofibromatosis or its associated features.

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Despite the rarity of recurrent benign schwannomatosis, there are many well-documented recurrence reports in patients treated for malignant peripheral nerve sheath tumors, specifically the malignant epitheliod variant of schwannoma.[7-9] A malignant peripheral nerve sheath tumor is defined as a malignant tumor of any cell type that arises from the nerve sheath. These tumors are of variable histology and most commonly are associated with neurofibromatosis type 1 (NF-1) or prior history of irradiation.[8] Manganoni and colleagues documented a review of patients receiving excisional biopsy for malignant peripheral nerve sheath tumors. In this series, it was demonstrated that 7 out of 25 patients (28%) who underwent tumor excision experienced a local recurrence.[8] Rayatt and colleagues[7] reported a case of a 74-year-old female patient who presented with malignant schwannoma, diagnosed via immunohistochemistry. Following excisional biopsy, the patient experienced 2 separate recurrences over a 21-month period.[7] Reports have shown that a previously documented benign schwannoma may convert to the malignant variant, resulting in metastases and local recurrence.[10] Whether a recurrent case of benign schwannomatosis is more likely to undergo malignant transformation is yet unknown.

Schwannomas and schwannomatosis occur equally in men and women and most often present between the second and fifth decades of life with symptoms of intractable pain persisting for multiple years before diagnosis and treatment.[11] These benign nerve sheath tumors may present as symptomatic masses, or they may produce neurologic deficits, depending on their location. They have been reported to occur at any somatic or visceral site, thus their distribution along nerve fibers. In fact, schwannomatosis has been reported in a variety of locations, such as the ankle; infratemporal fossa; cranial nerves; gluteal, paraspinal, mediastinal/retroperitoneal regions; neck; wrist; and hand.[2,5,11-15]

The tumors of schwannoma, whether single or multifocal, generally consist of a globoid mass, usually less than 5 cm, surrounded by an epineurium capsule. On cut section, the tumors have a mixture of gray-white fibrous tissue and bright yellow foci. Microscopically, schwannomas classically contain an area of densely packed spindle cells, called Antoni A areas, which may include nuclear palisading, whirling of cells, and Verocay bodies.[16] The Antoni A areas are intermixed with looser, less orderly, myxoid regions, called Antoni B tissue.[16] Also characteristic of the schwannoma are large, irregularly spaced vessels, which are most prominent in the Antoni B areas.[16] The tumor cell cytoplasm may stain for S-100 protein, which may assist in diagnosis.[7]

Since MacCollin and colleagues[3,17] first considered schwannomatosis to be a distinct clinical entity separate from NF-2, schwannomatosis since has become a newly recognized classification of neurofibromatosis. The genetic loci associated with schwannomatosis and NF-2 are each found on chromosome 22; however, they are located at sites distant from one another.[18] In light of this close genetic association, there could be a yet undiscovered link between recurrence of schwannoma in NF-2 and benign recurrent schwannomatosis.

Much less is known about schwannomatosis, and the understanding of this entity is only recently emerging in the literature. Though the lesions in schwannomatosis are molecularly distinct from those found in classic neurofibromatosis, it may be difficult to differentiate them clinically because of their similar presentation as peripheral nerve sheath tumors.

Radiologically, tumors in schwannomatosis are the same as those of schwannoma, except multiplicity at different anatomic locations. Schwannomas are iso- or slightly hypodense on nonenhanced CT scan. Small tumors usually show uniform enhancement, while larger lesions may have a heterogenous pat-

tern. On T_1-weighted MRI, a rim of fat around the tumor, known as the split fat sign, may be identified.[19] T_2-weighted MRI may show the characteristic "target sign" consisting of a very thin rim of hyperintensity, corresponding to tumor capsule, surrounding a central area of hypointensity.[1,2,19] Some studies have noted the difference in distribution that may help characterize and further differentiate schwannomatosis and neurofibromatosis. It has been reported that the tumors in schwannomatosis are distributed segmentally, whereas the tumors of neurofibromatosis are distributed in a more continuous pattern.[3]

Although the lesions in schwannomatosis are benign, a confirmatory histologic diagnosis always must be made to differentiate multiple benign schwannomas from malignant variants or disorders that may present with peripheral nerve sheath tumors, such as neurofibromatosis. Unlike benign schwannoma and schwannomatosis, which are composed entirely of schwann cells, the nerve sheath tumors in neurofibromatosis are of mixed origin, containing schwann cells, mast cells, lymphocytes, perineural-like cells, and fibroblasts.[20]

Treatment also differs when comparing schwannomatosis and neurofibromatosis. Because of its benign nature, schwannomatosis often may be treated conservatively, unless causing symptomatic pain, while neurofibromatosis may require monitoring for malignant transformation. The prognosis of either benign solitary schwannoma or schwannomatosis is excellent with a less than 5% recurrence rate after excisional biopsy.[20]

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

References

1. Yamamoto T, Maruyama S, Mizuno K. Schwannomatosis of the sciatic nerve. *Skeletal Radiol.* 2001;30(2):109-113.
2. Huang J, Mobbs R, Teo C. Multiple schwannomas of the sciatic nerve. *J Clin Neurosci.* 2003;10(3):391-393.
3. MacCollin M, Chiocca EA, Evans DG, et al. Diagnostic criteria for schwannomatosis. *Neurology.* 2005;64(11):1838-1845.
4. Louis DN, Ramesh V, Gusella JF. Neuropathology and molecular genetics of neurofibromatosis 2 and related tumors. *Brain Pathol*. 1995;5(2):163-172.
5. Huang JH, Simon SL, Nagpal S, Nelson PT, Zager EL. Management of patients with schwannomatosis: report of six cases and review of the literature. *Surg Neurol*. 2004;62(4):353-361.
6. Isenberg JS, Mayer P, Butler W, Pfaff-Amesse T, Persing JA. Multiple recurrent benign schwannomas of deep and superficial nerves of the upper extremity: a new variant of segmental neuro fibromatosis. *Ann Plast Surg*. 1994;33(6):659-663.
7. Rayatt SS, Jones ME, Powell BW. Surgical treatment of locally recurrent malignant schwannoma of the lower leg. *Br J Plast Surg.* 1999;52(4):317-319.
8. Manganoni AM, Farisoglio C, Lonati A, Zorzi F, Tucci G, Pinton PG. Cutaneous epithelioid malignant schwannoma: review of the literature and case report. *J Plast Reconstr Aesthet Surg.* 2009;62(9):e318-e321.
9. Laskin WB, Weiss SW, Bratthauer GL. Epithelioid variant of malignant peripheral nerve tumor (malignant epithelioid schwannoma). *Am J Surg Pathol.* 1991;15(12):1136-1145.
10. Woodruff JM, Selig AM, Crowley K, Allen PW. Schwannoma (neurilemoma) with malignant transformation. A rare, distinctive peripheral nerve tumor. *Am J Surg Pathol*. 1994;18(9):882-895.
11. Hasham S, Matteucci P, Stanley PR. Schwannomatosis: multiple schwannomas of the upper limb. *J Hand Surg Br.* 2006;31(2):182-184.
12. Harbaugh K, Smith P, Towfighi J. Schwannomatosis in a patient with a pelvic mass: case report. *Neurosurg Focus.* 2007;22(6):E8.
13. Kim DH, Hwang JH, Park ST, Shin JH. Schwannomatosis involving peripheral nerves: a case report. *J Korean Med Sci.* 2006;21(6):1136-1138
14. Ellis SJ, Gordin S, Edgar MA, Morris CD. Multiple ipsilateral lower extremity masses in a 46-year-old man. Schwannomatosis. *Clin Orthop Relat Res.* 2007;(456):268-274.
15. Westhout FD, Mathews M, Pare LS, Armstrong WB, Tully P, Linskey ME. Recognizing schwannomatosis and distinguishing it from neurofibromatosis type 1 or 2. *J Spinal Disord Tech*. 2007;20(4):329-332.
16. Weiss SW, Goldblum JR, eds. *Enzinger and Weiss's Soft Tissue Tumors*. 4th ed. St. Louis, MO: Mosby; 2001.
17. MacCollin M, Willett C, Heinrich B, et al. Familial schwannomatosis: exclusion of the NF2 locus as the germline event. *Neurology*. 2003;60(12):1968-1974.
18. Kaufman DL, Heinrich BS, Willett C, et al. Somatic instability of the NF2 gene in schwannomatosis. *Arch Neurol*. 2003;60(9):1317-1320.
19. Pilavaki M, Chourmouzi D, Kiziridou A, Skordalaki A, Zarampoukas T, Drevelengas A. Imaging of peripheral nerve sheath tumors with pathologic correlation: pictorial review. *Eur J Radiol*. 2004;52(3):229-239.
20. Huang JH, Johnson VE, Zager EL. Tumors of the peripheral nerves and plexuses. *Curr Treat Options Neurol.* 2006;8(4):299-308.