Schwannomatosis in a patient with a pelvic mass

Case report

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✓ Schwannomatosis is the most recently recognized form of neurofibromatosis in which patients harbor multiple non-vestibular nerve schwannomas. The diagnosis is contingent on excluding neurofibromatosis Type 2 (NF2), to which it is related. The authors present a case of schwannomatosis diagnosed fortuitously when a preoperative magnetic resonance (MR) image of a pelvic schwannoma was suggestive of a lesion in the lower lumbar canal. Definitive studies confirmed the presence of multiple spinal tumors including a thoracic schwannoma, which was removed during a subsequent procedure. This case emphasizes the need to consider the possibility of multiple tumors in every patient presenting with a schwannoma because the follow-up and genetic counseling are vastly different in those with NF2 and schwannomatosis compared with those harboring sporadic tumors. Details of this case and current considerations in the diagnosis and management of schwannomatosis are discussed.

KEY WORDS • multiple schwannomas • neurilemma • neurofibromatosis Type 2 • schwannomatosis

WHEREAS most benign schwannomas occur sporadically, approximately 4% of patients in larger studies will harbor multiple tumors.^{2,11,17,25} In some smaller series of schwannomas limited to the hand or extremities, multiple tumors have been noted in 12 to 28% of patients.^{15,26,28,30} The differential diagnosis in a patient with multiple schwannomas includes primarily NF2 and schwannomatosis, which is the most recently recognized form of neurofibromatosis in which patients harbor multiple non-vestibular nerve schwannomas. Despite the fact that criteria for diagnosis were initially suggested in 1997¹³ and subsequently revised in a recently published consensus statement,²¹ the term “schwannomatosis” continues to be used to describe the occurrence of multiple schwannomas in any one patient.¹⁰ Given the differences in the two disease processes—in particular with respect to associated tumors, decreased life expectancy, and increased risk of familial transmission in patients with NF2³—the term “schwannomatosis” should be carefully applied. We present a case of schwannomatosis diagnosed fortuitously when a preoperative MR image of a pelvic schwannoma was suggestive of

a lesion in the lower lumbar canal. We also present current considerations in the diagnosis and management of schwannomatosis.

Case Report

History. This 50-year-old woman underwent total abdominal hysterectomy for removal of an enlarged uterus and a history of menorrhagia-induced anemia. Three months later, the presence of a left pelvic mass was confirmed on ultrasonography. The patient underwent reoperation at an outside facility for a presumed hematoma. A retroperitoneal mass was encountered, the hematoma was evacuated, and additional brisk bleeding was noted and controlled. Pathological inspection of samples obtained at surgery revealed a hematoma and tissue fragments consistent with schwannoma. Postoperatively, she had severe exacerbation of longstanding left hip and radicular leg pain.

Examination. She was referred to the Penn State Milton S. Hershey Medical Center for definitive treatment. Pain in the left hip region extended into the posterior left leg and foot diffusely without associated sensory or motor symptoms. She reported no bowel and bladder symptoms except for longstanding mild stress incontinence. She had no personal

Abbreviations used in this paper: MR = magnetic resonance; NF2 = neurofibromatosis Type 2.

FIG. 1. Axial contrast-enhanced MR image demonstrating the large enhancing mass in the left lumbosacral plexus.

or family history of nerve sheath tumors. She had no visual or auditory symptoms. Annual hearing tests performed at her place of employment had been consistently normal. Prior ophthalmological examinations had been normal. On clinical examination, she had no cutaneous lesions or palpable nodules along the course of her peripheral nerves. A neurological examination was normal. No pathological reflexes were identified. Preoperative MR imaging studies of the pelvis revealed a $7 \times 6 \times 5$ -cm mass in the left lumbosacral plexus with a central focus of hemorrhage and heterogeneous contrast enhancement (Fig. 1). An 8-mm enhancing lesion was noted in the subgluteal plane near the lesser trochanter, and another lesion was suspected to be within the lumbar canal at the L-5 level.

Operation. A multidisciplinary team performed excision of the pelvic mass. Because of adhesions, a sigmoid colectomy was performed, allowing access to the tumor. With the assistance of neuromonitoring, the tumor was excised by carefully dissecting the lumbar plexal elements from the tumor capsule.

Postoperative Course. Neuropathological evaluation of the tissue revealed findings consistent with benign schwannoma (Fig. 2). There was extensive hemorrhage and necrosis but a low mitotic rate and only mild pleomorphism. Vascular hyalinization was also noted. The tumor stained diffusely positive for S100 protein.

The patient was noted to have intermittent mild left lateral thigh and foot paresthesias and a small area of left foot numbness. These symptoms resolved over several months. She had no weakness or other neurological symptom. The left hip and leg pain completely resolved and have not returned. Her postoperative course was complicated by an ileus requiring a brief readmission but no longstanding sequelae. Cranial imaging, including an internal auditory canal protocol, revealed no abnormalities. Spinal imaging confirmed the presence of multiple tumors in the lumbosacral canal (Fig. 3). In addition, an intradural, extramedullary, enhancing lesion at the T-7 region was noted to cause significant cord compression (Fig. 4).

Second Surgery and Postoperative Course. Because of the associated canal compromise and slight increase in her lower-extremity reflexes, the patient underwent thoracic laminectomy, microsurgical removal of the T-7 lesion, and

FIG. 2. Photomicrograph revealing a pelvic schwannoma through a compact Antoni A area. Note the palisading of nuclei. H & E.

neuromonitoring 9 months after excision of the pelvic schwannoma. At surgery, the tumor was noted to arise from a dorsal rootlet and was easily separated from the underlying flattened spinal cord. She tolerated the procedure well without complication. Pathological studies again revealed a benign schwannoma with Antoni A and B areas (Fig. 5) and diffuse staining for the S100 protein. Eighteen months

FIG. 3. Sagittal T1-weighted Gd-enhanced MR image through the lumbosacral region demonstrating multiple enhancing lesions within the canal at L1–2 and L-5. Note the additional areas of punctate enhancement along the cauda equina.

FIG. 4. Sagittal T1-weighted Gd-enhanced (*upper*) and axial T2-weighted non-contrast-enhanced (*lower*) MR images through the thoracic region showing the intradural extramedullary lesion occupying the posterior two thirds of the spinal canal and causing significant cord compression.

after the initial procedure, she remained neurologically intact without symptoms. Spinal imaging repeated 1 year after the initial studies revealed no change in the remaining lumbar canal lesions.

Discussion

Multiple Compared With Solitary Schwannomas

This case emphasizes the need to consider the possibility of multiple tumors in every patient with schwannoma. Although most schwannomas are thought to occur in isolation, the percentage of patients with multiple lesions in clinical series of schwannomas has varied widely. In larger surgical studies of spinal and peripheral schwannomas (70–

FIG. 5. Photomicrograph of the thoracic schwannoma demonstrating compact Antoni A (*upper*) and loose Antoni B (*lower*) areas. H & E.

246 cases), multiple tumors have been noted in 0 to 6% of patients.^{2,11,17,18,25} Some of the studies specifically focused on schwannomatosis have attempted to exclude patients with NF2.^{11,17} Given that NF2 and schwannomatosis are thought to occur with a similar frequency,¹ however, the actual percentage of patients with multiple tumors in the series overall is likely to be higher than reported. In a population-based study from Finland, multiple schwannomas were noted in 5% of cases.¹ The authors of that study as well as others have pointed out that the number of peripheral tumors was likely underestimated given that mandatory reporting was required for cranial and spinal lesions only.^{1,9}

In contrast, there are several smaller (16–32 patients) surgical analyses of extremity schwannomas in which patients with multiple tumors have comprised 12 to 28% of cases.^{15,26,28,30} In one study, 18 patients with hand and wrist schwannomas were identified from a pathophysiology database of 280 schwannomas at one hospital between 1991 and 1997.²⁸ In this population, five patients (28%) had undergone removal of schwannomas in other areas of the body, and two of the five had multiple tumors in the hand. Whether this finding represents the true incidence of multiple schwannomas or simply indicates a propensity for patients with multiple tumors to have them in the hand and wrist region is not clear. In some centers, whole-body MR imaging is being used as a research tool to assess tumor burden in patients with neurofibromatosis and schwannomatosis.⁹ A prospective study of whole-body MR imaging in a group of patients with solitary schwannomas may better reveal the likelihood of multiple tumors. Outside the research setting, a whole-body screening approach is impractical and unnecessary.

Neurofibromatosis Type 2 Compared With Schwannomatosis

In patients harboring multiple schwannomas, the differential diagnosis includes NF2, schwannomatosis, and other very rare conditions such as Carney complex.^{7,9,19,21} For practical purposes, the initial concern relates to determining whether the patient has NF2. The diagnostic criteria for

NF2 are well established.⁸ The diagnosis of definite NF2 is made in a patient with bilateral vestibular schwannomas or in one with a first-degree family member with NF2 and who either is younger than 30 years old and harboring a unilateral vestibular schwannoma or has two or more of the following abnormalities: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities, or juvenile cortical cataract. Presumptive NF2 is diagnosed in a patient under the age of 30 years with a unilateral vestibular schwannoma and at least one of the tumors/ocular abnormalities listed, or in any person with two or more meningiomas and either a unilateral vestibular schwannoma or one of the tumors/ocular abnormalities listed.

Detailed medical and family history, physical examination, ophthalmological examination, and craniospinal imaging that includes high-resolution assessment of the vestibular nerves are often sufficient for making the diagnosis of NF2.⁸ Although most patients with NF2 present with signs of vestibular nerve dysfunction, approximately 70% will have some evidence of peripheral involvement,^{9,23} and in younger patients or those with sporadic or mosaic forms of NF2, nonvestibular schwannomas and/or other NF2-associated tumors may be present before the development of the vestibular schwannomas.^{4,6,23}

The routine use of NF2 mutational analysis is controversial given that constitutional mutations are detected in only 65% of patients with bilateral vestibular schwannomas.^{4,21} The detection rate is lower in patients with NF2 who have mild disease and/or have somatic mosaicism.⁴ If a germline or constitutional NF2 mutation is detected, however, schwannomatosis is excluded (as discussed later).^{4,21} The 50-year-old patient in the present case with normal cranial MR imaging and a negative family history did not fulfill the criteria for an NF2 diagnosis. For this reason, NF2 mutational analysis was not performed.

Diagnostic Criteria for Schwannomatosis

The diagnosis of schwannomatosis is based on clinical criteria. In recent years, longitudinal studies of NF2, routine use of high-quality MR imaging, and advances in genetic techniques have led to a better understanding of NF2 and schwannomatosis.^{6,16,22} Many patients from previously published studies of schwannomatosis were found to have NF2.^{23,24,27,29} For this reason, clinical criteria initially proposed in 1997 by Jacoby et al.¹³ for the diagnosis of schwannomatosis were revised in a consensus statement published in 2005.²¹ The changes relate primarily to increasing the age at which the diagnosis of schwannomatosis is considered and the recommended use of high-quality MR imaging for the exclusion of vestibular tumors. The patient in the present case clearly meets the current criteria for definite schwannomatosis as outlined in the consensus statement and summarized in the subsequent paragraphs.

The diagnosis of definite schwannomatosis can be made in patients over the age of 30 years who have two or more nonintradural schwannomas, at least one of which is pathologically confirmed, and a high-quality MR image excluding the presence of vestibular schwannoma. Patients younger than 30 years old but who otherwise fulfill the aforementioned criteria are categorized as having possible schwannomatosis. Patients with a first-degree relative who meets the aforementioned criteria for definite schwanno-

matosis and who have at least one pathologically confirmed nonvestibular schwannoma can also be considered to have definite schwannomatosis.

Moreover, patients can be considered to have possible schwannomatosis if they are older than 45 years of age with two or more nonintradural schwannomas, at least one of which is pathologically confirmed, and have no symptoms of eighth cranial nerve dysfunction. Possible schwannomatosis can also be considered in patients with a nonvestibular schwannoma according to a radiographic study and a first-degree relative who meets the criteria for definite schwannomatosis. Segmental schwannomatosis is diagnosed in patients who meet the aforementioned criteria but who have tumors limited to one limb or five or fewer spinal segments.

As noted previously, although NF2 mutational testing is not required,^{4,21} patients who undergo testing and are found to have a known constitutional NF2 mutation are excluded from the diagnosis of schwannomatosis.

Citing a number of clinical examples in which patients fit the criteria for both NF2 and schwannomatosis, Baser et al.⁴ recommended an additional revision to the criteria: schwannomatosis should be excluded in patients who meet the existing criteria for NF2 or have a first-degree relative with NF2. Moreover, they estimate that 24% of patients with NF2 as well as unidentified mutations and 11% of those with somatic mosaicism will experience vestibular symptoms after the age of 45 years, and thus recommend the absence of vestibular schwannoma on high-quality MR imaging and not just the absence of vestibular nerve symptoms for the possible schwannomatosis category.⁴

Clinical Considerations in Schwannomatosis

Characteristics of patients with schwannomatosis are similar to those in groups with solitary lesions, that is, no sex predilection and a mean age in the mid 40s at presentation.^{1,2,11,29} Patients often present with pain that can be chronic and debilitating.^{9,21} Segmental cases in which tumors are limited to one region of the body, such as an extremity or spine, account for approximately one third of cases.^{1,13,21,23} Unlike in NF2, there is no tendency for the development of ocular abnormalities or other nonschwannoma lesions such as meningioma or glioma, and life expectancy is unaffected.²¹ Familial transmission is noted in a minority of cases, and when present there is an autosomal-dominant pattern with incomplete penetrance and variable expressivity.^{1,21,22} Benign peripheral schwannomas have no propensity to malignant degeneration and therefore do not need to be removed or serially imaged unless symptomatic. Symptomatic spinal lesions and those demonstrating growth or causing significant cord compromise may need to be excised.^{11,21,29} The likelihood of new tumor development and growth is variable.^{5,21,29} In one series a lumbar spinal lesion remained unchanged over 14 years of observation.²⁹ Most lesions can be removed safely, although new neurological deficits after tumor excision have been reported.^{12,29} Genetic counseling should be considered and patients should be checked regularly with instructions to monitor themselves for the development of neurological symptoms.

Genetic Considerations

Although the truncating mutations of the NF2 gene seen in tumors from patients with schwannomatosis do not differ

from those in patients with sporadic schwannomas or NF2,¹³ multiple lesions removed from an individual with schwannomatosis do not demonstrate uniform mutational abnormalities, as in patients with NF2.^{14,16,20,22} This finding, along with a lack of NF2 germline mutations in patients with schwannomatosis, provides evidence that the disorder is distinct from NF2.^{14,16,22} Recent study data suggest the presence of a gene centromeric or proximal to the NF2 gene on chromosome 22q, which may be responsible for the development of the somatic instability noted in patients with schwannomatosis.^{9,22} Future studies comparing peripheral solitary schwannomas with those from patients with schwannomatosis and NF2 will likely be required to further define the genetic mechanisms responsible for the development of multiple tumors.²¹ Ensuring that solitary tumors are in fact "solitary" will be important in this regard.

Conclusions

This case emphasizes the need to consider the possibility of multiple tumors in every patient presenting with a benign schwannoma because the natural history, follow-up, and genetic counseling are vastly different in patients with NF2 and schwannomatosis in comparison with patients with sporadic tumors. The precise genetic mechanisms responsible for the development of multiple tumors in schwannomatosis remain unknown.

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Manuscript submitted March 15, 2007.

Accepted April 24, 2007.

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