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Clinical Features of Schwannomatosis: A Retrospective Analysis of 87 Patients

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ABSTRACT

Background. **Schwannomatosis is a recently recognized form of neurofibromatosis characterized by multiple noncutaneous schwannomas, a histologically benign nerve sheath tumor. As more cases are identified, the reported phenotype continues to expand and evolve. We describe the spectrum of clinical findings in a cohort of patients meeting established criteria for schwannomatosis.**

Methods. **We retrospectively reviewed the clinical records of patients seen at our institution from 1995–2011 who fulfilled either research or clinical criteria for schwannomatosis. Clinical, radiographic, and pathologic data were extracted with attention to age at onset, location of tumors, ophthalmologic evaluation, family history, and other stigmata of neurofibromatosis 1 (NF1) or NF2.**

Results. **Eighty-seven patients met the criteria for the study. The most common presentation was pain unassociated with a mass (46%). Seventy-seven of 87 (89%) patients had peripheral schwannomas, 49 of 66 (74%) had spinal schwannomas, seven of 77 (9%) had nonvestibular intracranial schwannomas, and four of 77 (5%) had intracranial meningiomas. Three patients were initially diagnosed with a malignant peripheral nerve sheath tumor; however, following pathologic review, the diagnoses were revised in all three cases. Chronic pain was the most common symptom (68%) and usually persisted despite aggressive surgical and medical management. Other common diagnoses included headaches, depression, and anxiety.**

Conclusions. **Peripheral and spinal schwannomas are common in schwannomatosis patients. Severe pain is difficult to treat in these patients and often associated with anxiety and depression. These findings support a proactive surveillance plan to identify tumors by magnetic resonance imaging scan in order to optimize surgical treatment and to treat associated pain, anxiety, and depression.** ***The Oncologist*** 2012;17:1317–1322

INTRODUCTION

Schwannomatosis is the third major form of neurofibromatosis, a group of neurogenetic disorders that share a predisposition to multiple nerve sheath tumors. The condition was initially thought to represent a mild form of neurofibromatosis 2 (NF2) because early series included patients with multiple peripheral schwannomas [1]. Research criteria for schwannomatosis were proposed in 1997 [2], and by 2003, it was clear that schwannomatosis was clinically and genetically distinct from NF2 [3]. In 2005, consensus diagnostic criteria for schwannomatosis were adopted for clinical use [4, 5], and these were modified the following year to specifically exclude patients who fulfilled the NF2 diagnostic criteria—bilateral vestibular schwannomas on high-quality magnetic resonance imaging (MRI), first-degree relative with NF2, or a known constitutional *NF2* mutation [5].

Schwannomatosis is uncommon, with an annual incidence of 0.58 cases per 1,000,000 persons [6]. As more cases are identified, the reported phenotype continues to expand and evolve. For example, recent case reports indicate that menin-

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Table 1. Criteria for definite and presumptive schwannomatosis

Diagnosis	Research criteria (1997) [1]	Consensus criteria (2005) [4]	Revised clinical criteria[a] (2006) [5]
Definite	• Two or more pathologically sampled schwannomas; lack of radiographic evidence of vestibular nerve tumor on an imaging study performed after age 18 years	• Age >30 years and two or more nonintradermal schwannomas, at least one with histologic confirmation, and no evidence of vestibular tumor on high-quality MRI scan and no known constitutional *NF2* mutation **OR**	• Age >30 years and two or more nonintradermal schwannomas, at least one with histologic confirmation **OR**
		• One pathologically confirmed nonvestibular schwannoma plus a first-degree relative who meets the above criteria	• One pathologically confirmed schwannoma plus a first-degree relative who meets the above criteria
Presumptive	• Two or more pathologically sampled schwannomas without symptoms of eighth nerve dysfunction at age >30 years **OR**	• Age <30 years and two or more nonintradermal schwannomas, at least one with histologic confirmation, and no evidence of vestibular tumor on high-quality MRI scan and no known constitutional *NF2* mutation **OR**	• Age <30 years and two or more nonintradermal schwannomas, at least one with histologic confirmation **OR**
	• Two or more pathologically sampled schwannomas in an anatomically limited distribution without symptoms of eighth nerve dysfunction at any age	• Age >45 years and two or more nonintradermal schwannomas, at least one with histologic confirmation, and no symptoms of eighth nerve dysfunction and no known constitutional *NF2* mutation **OR**	• Age >45 years and two or more nonintradermal schwannomas, at least one with histologic confirmation **OR**
		• Radiographic evidence of a nonvestibular schwannoma and first degree relative meeting the criteria for definite schwannomatosis	• Radiographic evidence of a schwannoma and first-degree relative meeting the criteria for definite schwannomatosis

[a]For the revised clinical criteria, all patients must not fulfill any of the existing sets of diagnostic criteria for NF2 and have no evidence of vestibular schwannoma on high-quality MRI scan, no first-degree relative with NF2, and no known constitutional *NF2* mutation.
Abbreviations: MRI, magnetic resonance imaging; NF2, neurofibromatosis 2.

giomas and malignant peripheral nerve sheath tumors (MPNSTs) occur in the setting of schwannomatosis [7–10]. Reports on clinical findings in large cohorts of patients with long follow-up are therefore essential for our understanding of the disease phenotype. In this report, we describe the spectrum of clinical findings in 87 patients meeting the criteria for schwannomatosis in a tertiary neurofibromatosis clinic.

Methods

The clinical records of patients seen at The Family Center for Neurofibromatosis at Massachusetts General Hospital (MGH) in 1995–2011 were retrospectively reviewed. Patients who fulfilled either the research criteria (used prior to 2005) [1], consensus diagnostic criteria [4], or modified diagnostic criteria [5] for schwannomatosis (Table 1) were included in the study. Clinical, radiographic, and pathologic data were extracted from clinical records with specific attention to age at onset, location of tumors, ophthalmologic evaluation, family history, and other stigmata of NF1 or NF2. All patients were examined by a neurologist in the neurofibromatosis clinic at MGH. This retrospective study was approved by the Massachusetts General Hospital institutional review board.

Results

Diagnostic and Research Criteria

Eighty-seven patients who met either the research or diagnostic criteria for schwannomatosis were identified. Sixty patients (69%) met the research criteria for definite, presumptive, or probable schwannomatosis; 27 did not meet the research criteria based on having only one pathologically proven schwannoma. Eighty patients (92%) met the criteria for presumptive or definite schwannomatosis based on the consensus diagnostic criteria. Seven patients did not meet the consensus diagnostic criteria as a result of a lack of high-quality MRI scan in a patient aged <45 years. Sixty-six patients (76%) met the more restrictive modified diagnostic criteria; 21 patients did not meet the modified criteria as a result of a lack of an internal auditory canal protocol on MRI scan. None of the 87 patients met the diagnostic criteria for NF1 or NF2.

Patient Characteristics

Of the 87 patients meeting the research or diagnostic criteria, 46 (53%) were female. The median age at initial symptom was 30 years (range, 8–59 years). The median age at diagnosis was 40 years (range, 16–70 years), with a median delay from initial symptom to diagnosis of 7 years (range, 0–39 years). A family history of schwannomatosis was present in 11 individuals (13%) from seven different families. Fifty patients (57%) initially presented with pain, including 40 (46%) unassociated with a mass and 10 (11%) associated with a mass. Thirty-six patients (41%) presented with a mass, including 24 (27%) with a painless mass, 10 with a painful mass (11%), and two (2%) whose tumor was found incidentally during other imaging. Nine patients (10%) experienced other symptoms, such as

numbness or weakness. In four patients (5%), the presenting symptoms were unknown.

Nervous System Tumors

Among 77 patients with cranial imaging, seven nonvestibular cranial schwannomas were identified in seven patients (8%) and five meningiomas were identified in four patients (5%). In contrast to NF2, no vestibular schwannomas were identified. Among 66 individuals with spinal imaging, spinal schwannomas were common (74%, 49 of 66). Spinal tumors were most common in the lumbar spine (53%, 35 of 66), followed by the thoracic spine (35%, 23 of 66), and cervical spine (23%, 15 of 66). Spinal tumors were most commonly localized to a single area of the spine (59%, 29 of 49), but in some patients they involved two areas (33%, 16 of 49) or the entire spine (8%, four of 49). In contrast to NF2, no intramedullary tumors suggestive of ependymoma were noted.

Peripheral schwannomas were present in most patients (89%, 77 of 87 patients), with the arms and legs being the most commonly affected sites (46% and 45%, respectively), followed by the head or neck (29%, 25 of 87), chest (16%, 14 of 87), pelvis (15%, 13 of 87), and abdomen (9%, eight of 87). Anatomically limited disease, defined as multiple schwannomas limited to a single limb or two spinal segments (Table 1), was present in 26 (30%) patients. The location of segmental involvement included the leg (35%), arm (23%), spine (23%), and other (19%, e.g., the pelvis).

Other Clinical Manifestations

Subcutaneous masses (presumed tumors) were identified by clinical examination in 23% of patients (20 of 87), with most presenting with one to five masses. In addition to schwannomas, pathologically proven lipomas were excised from 11 (13%) patients, angiolipomas were excised from three (3%) patients, and cutaneous neurofibromas were excised from two (2%) patients. Ophthalmologic abnormalities were present in a minority of patients who had formal examinations (18%, seven of 39) and included single cases of visual field defect, Addis pupil, red–green color blindness, unilateral juvenile cataract, amblyopia, indistinct hyperpigmentation, and undefined ophthalmologic stigmata of neurofibromatosis. Twenty patients (23%) had at least one café-au-lait macule that was >1.5 cm in size; no patient had more than four. No skinfold freckling was seen in these patients. Four patients had a history of learning disability (5%), five (6%) had an existing diagnosis of scoliosis, and 14 (16%) reported tinnitus.

Surgical Management

Eighty-six patients underwent 217 surgeries for schwannoma resection (median number of surgeries per patient, 2; range, 1–9). Forty patients underwent a total of 72 spinal surgeries, including 20 on the cervical spine (28%), 11 on the thoracic spine (15%), 30 on the lumbosacral spine (42%), and 11 on more than one spinal section (15%). Almost half of the patients (18 of 40, 45%) experienced persistent postoperative deficits, including sensory abnormalities in 13 patients, weakness in four patients, painful kyphosis or kyphoscoliosis in three patients, and bladder dysfunction in three patients. Seventy patients underwent 145 peripheral surgeries in locations spanning the entire body. Nineteen patients (27%, 19 of 70) had persistent postoperative deficits, including sensory abnormalities in 12 patients, weakness in five patients, and bladder dysfunction in one patient.

Prevalence and Management of Pain

The most common symptom reported by schwannomatosis patients was chronic pain (68%, 59 of 87 patients), which included both local and multifocal or diffuse pain. Sixteen patients (18%) were disabled by their pain and either had to take extended medical leave from work or were unable to work. Accordingly, pain was the indication for surgery in most patients (80%, 70 of 87) and for most surgeries (80%, 145 of 181) for which an indication for surgery was documented. Local pain was completely relieved in less than half of the surgeries (39%, 57 of 145) and recurred in most patients (75%, 43 of 57), either at the site of the original tumor or as a result of a new tumor. Local pain was partially relieved after 20 of 145 (14%) surgeries and was unchanged after 41 of 145 (28%) surgeries. The outcome on local pain relief was unknown for 27 of 145 (19%) surgeries.

Most patients (62%, 54 of 87) reported the use of medications for chronic pain at some point in their care. The median number of pain medications trialed was three (range, 1–15), with 72% of patients (39 of 54) reporting use of five or fewer medications, 20% of patients (11 of 54) reporting six to ten medications, and 7% of patients (four of 54) reporting >10 medications. An equal number of patients reported the use of neuropathic, opiate, and anti-inflammatory medications (63%, 34 of 54), most commonly gabapentin (24 of 54), oxycodone formulations (23 of 54), and amitriptyline (20 of 54). A minority of patients were treated with muscle relaxants (17%, nine of 54) or various other medications, including the lidocaine patch (19%, 10 of 54). Patients used a median of two concurrent medications (range, 1–6) for pain management. Other methods of pain control included spinal block (five patients), radiofrequency lesioning (two patients), and a transcutaneous electrical nerve stimulator unit (one patient). No patients were treated with chemotherapy.

Comorbid Conditions

Eleven patients (12.6%) were diagnosed with 16 malignancies. At initial pathologic review, three patients were diagnosed with MPNST and one patient was diagnosed with spindle cell carcinoma. Upon further review by one author with expertise in NF-related pathology (A.S.R.), the pathologic diagnosis was revised in all four cases. Two cases of MPNST were reclassified as cellular schwannomas based on their histological features and their diffuse, marked expression of S100 and p16 proteins on immunohistochemistry (Fig. 1B–D), one case of MPNST was reclassified as melanoma based on the presence of a characteristic *BRAF*^{V600E} mutation (that was also present in a coexistent primary skin melanoma), and one case of spindle cell carcinoma was not available for review but was presumed to be schwannoma based on the long survival of the patient after diagnosis (>35 years). The remaining malignan-

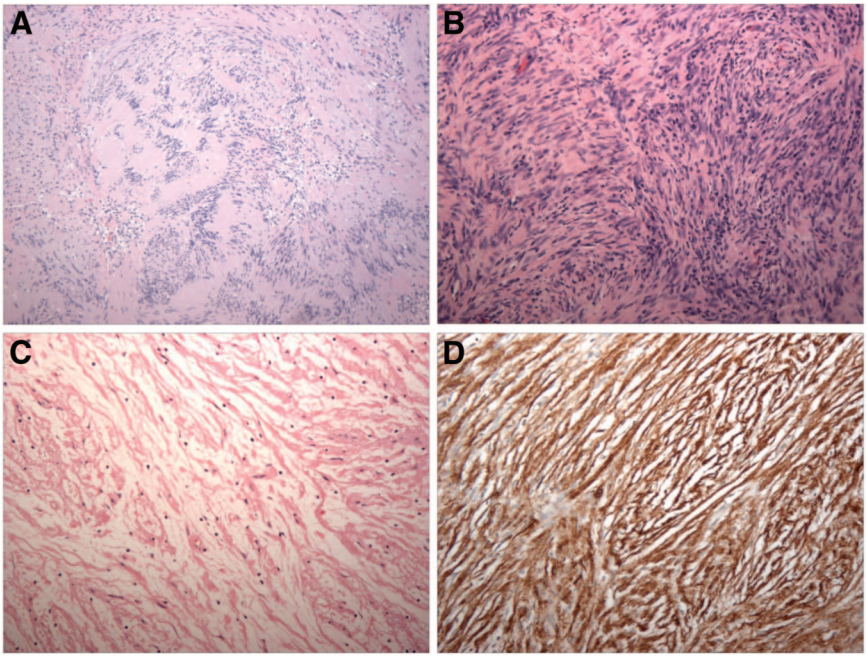

Figure 1. Histological misdiagnosis of schwannomas in a schwannomatosis patient. **(A):** Hemotoxylin and eosin (H&E) stain of a schwannoma with classic histology, including numerous Verocay body formations. **(B):** H&E stain of a cellular schwannoma. The tumor is moderately cellular, with mitoses and foci of necrosis and patternless, lacking Antoni A/Antoni B areas and Verocay bodies. This tumor can be misdiagnosed as low-grade malignant peripheral nerve sheath tumor. **(C):** H&E stain of schwannoma showing regions with prominent myxoid background. Myxoid schwannomas may be confused with neurofibromas. **(D):** Diffuse staining for S100 protein highlights the monotonous population of neoplastic Schwann cells composing the tumor, supporting the diagnosis of schwannoma.

cies included seven skin cancers (four basal cell carcinomas, two squamous cell carcinomas, and one melanoma), two papillary thyroid carcinomas, two breast cancers (one ductal carcinoma and one of unknown type), and one lung adenocarcinoma.

Fifty-two patients (60%) had cysts diagnosed clinically, pathologically, or radiographically. Fifteen patients (17.2%) had visceral cysts, including renal cysts ($n = 14$), hepatic cysts ($n = 3$), and a pancreatic cyst ($n = 1$). Thirteen of 46 women in the study (28%) had cysts in the ovaries and/or fallopian tubes. Other common cysts included mucus retention cysts in the maxillary sinuses; Baker's, subchondral, and synovial cysts in the joints; and epidermal cysts on the skin.

Twenty-six patients (30%) received clinical diagnoses of depression, including 18 of 46 women (39%) and seven of 41 men (17%). Eighteen patients (20%) reported migraines or frequent headaches, including 13 of 46 women (28%) and five of 41 men (12%). Eleven patients (13%) had diagnoses of hypothyroidism and were receiving levothyroxine. Of these, 10 of 46 (22%) were women and one of 41 (2%) was male.

Discussion

One of the main challenges in diagnosing schwannomatosis is to differentiate it from NF2 or NF1. Although none of the patients in our cohort simultaneously met the diagnostic criteria for NF1 or for NF2, careful attention to other clinical manifestations remains essential in establishing the correct diagnosis. Some NF2 patients may present with multiple peripheral schwannomas [11], making it critical to screen all suspected schwannomatosis patients for NF2. Schwannomatosis is characterized by the presence of multiple *nonvestibular, nonintradermal schwannomas*, whereas the hallmark of NF2 is the presence of *bilateral vestibular schwannomas*. The consensus diagnostic criteria and the revised diagnostic criteria address this issue by requiring cranial MRI scans to exclude vestibular schwannomas. However, a recent report from the Manchester group suggests that schwannomatosis patients may, in fact, develop unilateral vestibular schwannomas [12], further blurring the distinction between these two conditions. To date, neither cataracts, epiretinal membranes, nor spinal ependymoma have been described at a higher frequency in schwannomatosis patients. Similarly, schwannomatosis must be differentiated from NF1. A lack of cardinal features of NF1—skinfold freckling, greater than six café-au-lait macules, multiple cutaneous nerve sheath tumors, and Lisch nodules—is helpful in excluding a diagnosis of NF1 in these patients. Importantly, the presence of an intracranial meningioma or a cutaneous neurofibroma does not exclude a diagnosis of schwannomatosis.

This retrospective review of 87 patients describes the largest cohort of schwannomatosis patients to date and provides a comprehensive view of the disease phenotype. Our results extend previous findings in smaller case series [4, 8] and document the common and uncommon features associated with schwannomatosis. In our series, the high rates of peripheral schwannomas (89% of patients) and spinal schwannomas (74%) support a proactive surveillance plan for schwannomatosis patients in which neurological symptoms and signs are investigated using MRI to identify tumors. These studies can

distinguish between schwannoma-related pain and other common causes of pain that are not related to tumors (e.g., degenerative disc disease, arthritis, or plantar fasciitis). Follow-up MRI scans can be performed periodically based on clinical symptoms to monitor for the appearance of new tumors, changes in tumor size, and involvement of nearby structures.

In accordance with previous reports, the rate of anatomically limited disease was 30% [4]. However, because patients in this study did not receive whole-body MRI scans, asymptomatic tumors in other body regions might have been missed by regional MRI. Despite the high prevalence of schwannomas, the median delay in diagnosis was 7 years in our population, indicating the need for earlier recognition of symptoms.

Other clinical features associated with NF2 were also present in our patients. Intracranial meningiomas were identified in 5% of our cohort, as compared with an expected prevalence of ~50% in NF2 patients [13]. These tumors usually occurred as solitary tumors in schwannomatosis patients, whereas they are often multiple or confluent in NF2 patients. The presence of a meningioma in a schwannomatosis patient was noted in early patient series [3, 14], and recently multigenerational families with meningiomas and germline *SMARCB1* mutations have been described [9, 10]. Other tumors common in NF2—spinal meningiomas and ependymomas—were not found in this series. Finally, there was no common ophthalmologic pathology in schwannomatosis patients. This finding contrasts with that for NF2 patients, in whom cataracts are found in up to 80% of patients [15].

Chronic pain remains the hallmark of schwannomatosis. The majority of our patients (68%) experienced chronic pain, and a significant number were disabled by their pain. Despite aggressive management with surgery (99%) and pain medication (62%), most patients did not become pain free. Furthermore, 20% of patients (28% of women and 12% of men) experienced frequent headaches, which were often described as "migraines." Whether this reflects a misattribution of nonspecific pain from other body parts or a separate mechanism remains unclear. Referral to an experienced pain clinic is warranted for schwannomatosis patients with chronic pain.

Depression and anxiety are also common in schwannomatosis patients, with 39% of women and 17% of men reporting a history of these mood disorders. Survey data indicate that patients with schwannomatosis suffer impaired quality of life and higher rates of depression than the normal population [16]. It is likely that the stress of living with chronic pain, especially pain that is often undiagnosed for years, leads to greater psychosocial stress on these patients. Active surveillance for and treatment of mood disorders is a central aspect of patient care, and appropriate referrals to mind–body programs and psychiatric treatment is warranted.

There is concern of a higher risk for malignancy in patients with schwannomatosis, in particular for MPNSTs and atypical teratoid/rhabdoid tumors (AT/RTs), because these tumors have been reported in patients with familial schwannomatosis [7, 8]. In our cohort, three patients were diagnosed with MPNST on initial pathologic review. All three diagnoses were revised upon subsequent review, and during this process, we identified features that may cause pathologic misdiagnosis of schwannomatosis-related schwannomas. In one cellular schwannoma, morphological features of classic schwannoma (such as Antoni A and Antoni B regions and Verocay bodies as seen in Fig. 1A) were absent and dense cellularity and mitoses were present (Fig. 1B). This schwannoma contained prominent hyperchromatic, atypical nuclei resulting from ancient change that was misinterpreted as early malignant transformation in a neurofibroma. A second schwannoma with prominent myxoid background (myxoid schwannoma) was misdiagnosed as a neurofibroma (Fig. 1C). This error led to a clinical diagnosis of NF1 rather than schwannomatosis in this patient, and to misinterpretation of a subsequent specimen as malignant transformation of a neurofibroma rather than schwannoma. In both cases, diffuse expression of S100 protein on immunohistochemistry was helpful in highlighting the monotonous population of neoplastic Schwann cells comprising the tumor (Fig. 1D). Because loss of expression of p16 is often associated with early malignant transformation in neurofibromas, diffuse expression of p16 is also helpful in supporting the diagnosis of a benign lesion in difficult cases. A third MPNST was reclassified as melanoma based on the presence of a characteristic *BRAF* mutation that was also present in a pre-existing skin melanoma from the same patient. Distinguishing metastatic amelanotic melanoma from MPNST may be impossible based on histology alone because the two tumors share similar histological and immunohistochemical features. However, newer molecular analysis (e.g., the presence of characteristic *BRAF* mutations) can help distinguish these two entities. Thus, in our series of 87 schwannomatosis patients, none were diagnosed with MPNST or AT/RT upon careful review. Our results suggest that a diagnosis of MPNST in a schwannomatosis patient should be viewed with caution because the pathological diagnosis in some of these cases may be challenging.

We identified clinical findings of indeterminate significance in our patient population. For example, our cohort had relatively high rates of lipomas, multiple angiolipomas, visceral cysts, orthopedic cysts, and ovarian cysts. It is unclear whether this finding represents a predisposition to these types of lesions or a high identification rate as a result of the aggressive imaging and surgical approach used for schwannomatosis patients. Similarly, it is unclear whether the high rate of hypothyroidism in schwannomatosis patients (22%, versus 9% in the general population) reflects a true association or an artifact of additional testing performed in the course of medical care [17]. Additional research with other cohorts of schwannomatosis patients should help address these questions.

The main limitation of this study is its retrospective nature and single-institution basis. Clinical information was incomplete for some patients, particularly those referred to our clinic from distant locations, because these patients were most likely to seek consultation and diagnosis only, rather than extensive treatment and follow-up. A multicenter, prospective study is needed to gather more comprehensive information that is tailored to the clinical and research questions most pertinent to schwannomatosis. The Children's Tumor Foundation has sponsored an international schwannomatosis database that contains limited data on >225 patients worldwide (Amanda

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