Clinical Features of Schwannomatosis: A Retrospective Analysis of 87 Patients

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Study funding**:** Supported by the Harvard Medical School Center for Neurofibromatosis and Allied Disorders.

Keywords: schwannomatosis, schwannoma, nerve sheath neoplasm, malignant peripheral nerve sheath tumor, intractable pain

Abstract

Background: Schwannomatosis is a recently recognized form of neurofibromatosis characterized by multiple non-cutaneous 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 between 1995 and 2011 who fulfilled either research or clinical criteria for schwannomatosis. Clinical, radiographic, and pathologic data were extracted with attention to age of onset, location of tumors, ophthalmologic evaluation, family history, and other stigmata of NF1 or NF2.

Results: Eighty-seven patients met criteria for the study. The most common presentation was pain unassociated with a mass (46%). Peripheral schwannomas were present in 77/87 patients (89%), spinal schwannomas in 49/66 (74%), non-vestibular intracranial schwannomas in 7/77 (9%), and intracranial meningiomas in 4/77 (5%). Three patients were initially diagnosed with a malignant peripheral nerve sheath tumor (MPNST); however, following pathologic review, the diagnoses were revised in all 3 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 MRI scan in order to optimize surgical treatment and to treat associated pain, anxiety, and depression.

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) since 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 were modified the following year to specifically exclude patients who fulfill the NF2 diagnostic criteria (with bilateral vestibular schwannomas on high-quality 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 meningiomas and malignant peripheral nerve sheath tumors (MPNST) occur in the setting of schwannomatosis[7,8,9,10]. Reports on the 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 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) between 1995 and 2011 were retrospectively reviewed. Patients who fulfilled either 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 of 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 (IRB).

Results

Diagnostic and Research Criteria

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

Patient Characteristics

Of the 87 patients meeting research or diagnostic criteria, 46 (53%) were female. The median age of 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 7 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, ten with a painful mass (11%), and 2 (2%) whose tumor was found incidentally during other imaging. Nine patients (10%) experienced other symptoms such as numbness or weakness. In 4 patients (5%), the presenting symptoms were unknown.

Nervous system tumors

Among 77 patients with cranial imaging, 7 non-vestibular cranial schwannomas were identified in 7 patients (8%) and 5 meningiomas were identified in 4 patients (5%). In contrast with NF2, no vestibular schwannomas were identified. Among 66 individuals with spinal imaging, spinal schwannomas were common (74%, 49/66). Spinal tumors were most common in the lumbar spine (53%, 35/66), followed by thoracic spine (35%, 23/66), and cervical spine (23%, 15/66). Spinal tumors were most commonly localized to a single area of the spine (59%, 29/49) but in some patients involved two areas (33%, 16/49) or the entire spine (8%, 4/49). In contrast with NF2, no intramedullary tumors suggestive of ependymoma were noted.

Peripheral schwannomas were present in most patients (89%; 77/87 patients), with the arms and legs being most commonly affected (46% and 45%, respectively) followed by the head/neck (29%, 25/87), chest (16%, 14/87), pelvis (15%, 13/87), and

abdomen (9%, 8/87). Anatomically limited disease, defined as multiple schwannomas limited to a single limb or 2 spinal segments (Table 1), was present in 26 (30%) patients. The location of segmental involvement included leg (35%), arm (23%), spine (23%), other (19%, e.g. pelvis).

Other clinical manifestations

Subcutaneous masses (presumed tumors) were identified by clinical examination in 23% of patients (20/87) with most presenting with 1-5 masses. In addition to schwannomas, pathologically proven lipomas were excised from eleven (13%) patients, angiolipomas from three (3%), and cutaneous neurofibroma from two (2%). Ophthalmologic abnormalities were present in a minority of patients who had formal examinations (18%, 7/39), 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 1 café-au-lait macule that was larger than 1.5 cm in size; no patients had more than 4. No skin fold freckling was seen in these patients. Four patients had a history of learning disability (5%), 5 (6%) had an existing diagnosis of scoliosis, and 14 (16%) reported tinnitus.

Surgical Management

Eighty-six patients underwent 217 surgeries for resection of schwannoma (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 patients (18/40, 45%) experienced persistent post-operative deficits, including sensory abnormalities in 13 patients, weakness in 4, painful kyphosis or kyphoscoliosis in 3, and bladder dysfunction in 3. Seventy patients underwent 145 peripheral surgeries in locations spanning the entire body. Nineteen patients (27%, 19/70) had persistent post-operative deficits, including sensory abnormalities in 12 patients, weakness in 5, and bladder dysfunction in one.

Prevalence and Management of Pain

The most common symptom reported by schwannomatosis patients was chronic pain (68%, 59/87 patients) which included both local and multifocal/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%, 70/87) and for most surgeries (80%, 145/181) for which an indication for surgery was documented. Local pain was completely relieved in less than half of surgeries (39%, 57/145), and recurred in most patients (75%, 43/57) either at the site of the original tumor or due to a new tumor. Local pain was partially relieved after 20/145 (14%) surgeries, and was unchanged after 41/145 (28%) surgeries. The outcome on local pain relief was unknown for 27/145 (19%) surgeries.

Most patients (62%, 54/87) reported use of medications for chronic pain at some point in their care. The median number of pain medications trialed was 3 (range, 1 to 15) with 72% of patients (39/54) reported use of 5 or fewer medications, 20% of patients (11/54) reported six to ten medications, and 7% of patients (4/54) reported more than

ten medications. An equal number of patients reported use of neuropathic, opiate, and anti-inflammatory medications 63%, (34/54), most commonly gabapentin (24/54), oxycodone formulations (23/54) and amitriptyline (20/54). A minority of patients was treated with muscle relaxants (17%, 9/54) or various other medications including lidocaine patch (19%, 10/54). Patients used a median of 2 concurrent medications (range, 1 – 6) for pain management. Other methods of pain control included spinal block (5 patients), radiofrequency lesioning (2 patients), and a transcutaneous electrical nerve stimulator (TENS) unit (1 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 1 patient with spindle cell carcinoma. Upon further review by one author with expertise in NF-related pathology (ASR), the pathologic diagnosis was revised in all 4 cases. Two cases of MPNST were re-classified as cellular schwannomas based on their histological features and their diffuse, marked expression of S100 and p16 proteins on immunohistochemistry (Fig. 1b-d); 1 case of MPNST was reclassified as melanoma based on the presence of a characteristic $BRAF^{V600E}$ mutation (that was also present in a co-existent primary skin melanoma); and 1 case of spindle cell carcinoma was not available for review but was presumed to be schwannoma based on the long term survival of the patient after diagnosis (longer than 35 years). The remaining malignancies included 7 skin cancers (4 basal cell carcinomas, 2 squamous cell carcinomas, and 1 melanoma); 2 papillary thyroid carcinomas; 2 breast cancers (1

ductal carcinoma and one of unknown type) and 1 lung adenocarcinoma.

Fifty-two patients (60%) had cysts diagnosed clinically, pathologically, or radiographically. Fifteen patients (17.2%) had visceral cysts, including renal cysts (14), hepatic cysts (3), and a pancreatic cyst (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 18/46 women (39%) and 7/41 men (17%). Eighteen patients (20%) reported migraines or frequent headaches, including 13/46 women (28%) and 5/41 men (12%). Eleven patients (13%) had diagnoses of hypothyroidism and were receiving levothyroxine. Of these, 10/46 (22%) were women and 1/41 (2%) was male.

Discussion

One of the main challenges in diagnosing schwannomatosis is to differentiate it from NF2 or NF1. While none of the patients in our cohort simultaneously met 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 *non-vestibular, non-intradermal 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 increased frequency in schwannomatosis patients. Similarly, schwannomatosis must be differentiated from NF1. The lack of cardinal features of NF1—skin-fold freckling, greater than 6 café-au-lait macules, multiple cutaneous nerve sheath tumors, and Lisch nodules—are helpful in excluding a diagnosis of NF1 in these patients. Importantly, the presence of intracranial meningioma or 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[8,4] and documents the common and uncommon features associated with schwannomatosis. In our series, the high rate of peripheral schwannomas (89% of patients) and spinal schwannomas (74%) support a pro-active surveillance plan for schwannomatosis patients in which neurological symptoms and signs are investigated by 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, since 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 to an expected prevalence of about 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.[10,9] 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 non-specific 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 indicates 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 a chronic pain, especially pain that is often undiagnosed for years, leads to increased 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 for increased risk of malignancy in patients with schwannomatosis, in particular for MPNST and atypical teratoid/rhabdoid tumors (AT/RT) since these tumors have been reported in patients with familial schwannomatosis.[7,8] In our cohort, three patients were diagnosed with MPNST at initial pathologic review. All 3 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 due to 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 composing the tumor (Fig. 1D). As expression of p16 is often associated with early malignant transformation in neurofibromas, diffuse expression of p16 is also helpful in supporting 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 as the two tumors share similar histological and immunohistochemical features. However, newer molecular analysis (e.g., 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, as 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 whether it reflects high identification rate as a result of aggressive imaging and surgical approach for schwannomatosis patients. Similarly, it is unclear whether the high rate of hypothyroidism in schwannomatosis patients (22% vs. 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, as these patients were most likely to seek consultation and diagnosis only, rather than extensive treatment and follow-up. A multi-center, 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 greater than 225 patients worldwide (Amanda Bergner, personal communication). This valuable resource should help facilitate patient-based research on schwannomatosis patients over the next decade.

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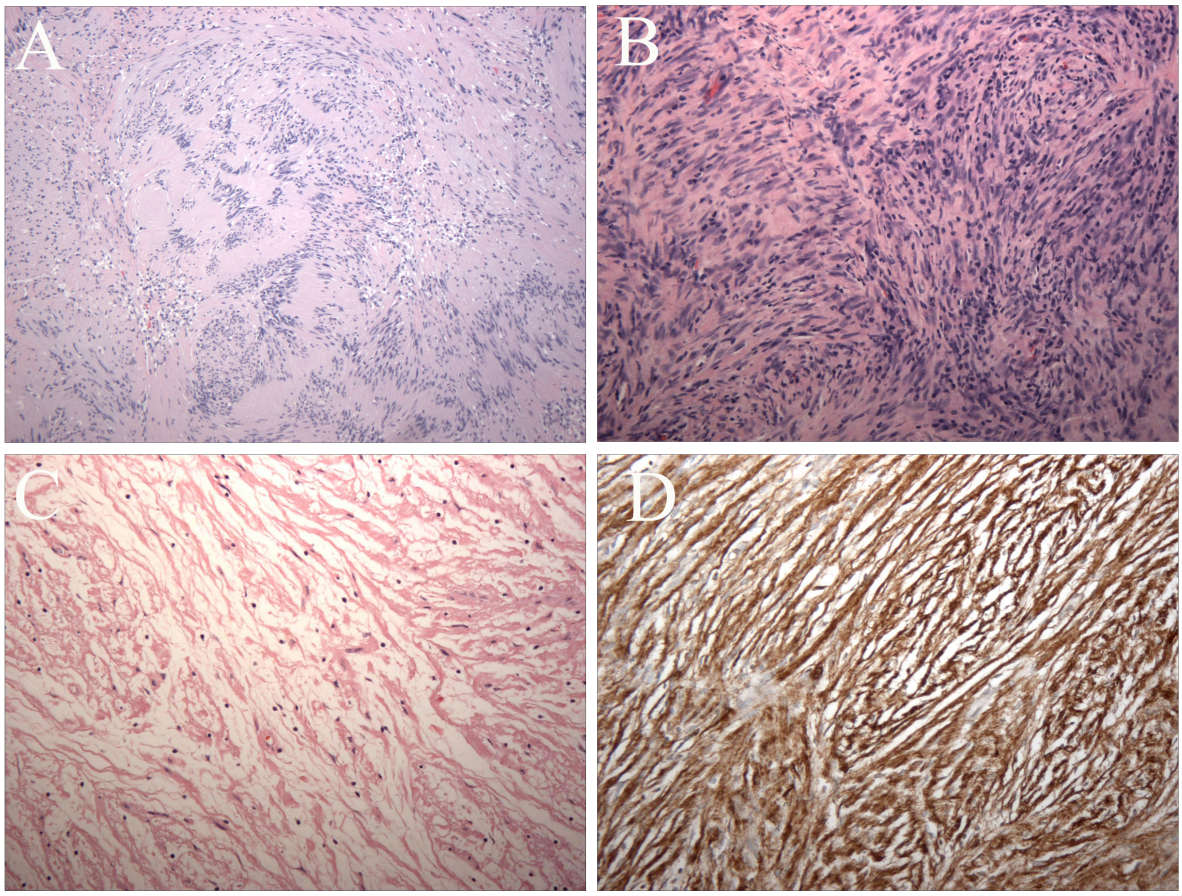
Table 1. Criteria for definite and presumptive schwannomatosis.

	Research Criteria[1] (1997)	**Consensus Criteria[4] (2005)**	**Revised Clinical Criteria[5] (2006)[a]**
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 non-intradermal schwannomas, at least 1 with histologic confirmation and no evidence of vestibular tumor on high-quality MRI scan and no known constitutional NF2 mutation **OR** • One pathologically confirmed non-vestibular schwannoma plus a first-degree relative who meets above criteria	• Age > 30 years and two or more nonintradermal schwannomas, at least one with histologic confirmation **OR** • One pathologically confirmed schwannoma plus a first-degree relative who meets the above criteria
Presumptive	• Two or more pathologically sampled schwannomas without symptoms of eight nerve dysfunction at age > 30 years **OR** • Two or more pathologically sampled schwannomas in an anatomically limited distribution without symptoms of eighth nerve dysfunction at any age	• Age < 30 years and two or more non-intradermal schwannomas, at least 1 with histologic confirmation and no evidence of vestibular tumor on high quality MRI scan and no known constitutional NF2 mutation **OR** • Age > 45 years and two or more non-intradermal schwannomas, at least 1 with histologic confirmation and no symptoms of 8th nerve dysfunction and no known constitutional NF2 mutation **OR** • Radiographic evidence of a non-vestibular schwannoma and first degree relative meeting criteria for definite schwannomatosis	• Age < 30 years and two or more nonintradermal schwannomas, at least one with histologic confirmation **OR** • Age > 45 years and two or more nonintradermal schwannomas, at least one with histologic confirmation **OR** • 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.

Figure 1. Histological misdiagnosis of schwannomas in a schwannomatosis patient.



Panel A: hemotoxylin and eosin (H&E) stain of a schwannoma with classic histology, including numerous Verocay body formations. Panel 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 MPNST. Panel C: H&E stain of schwannoma showing regions with prominent myxoid background. Myxoid schwannomas may be confused with neurofibromas. Panel D: Diffuse staining for S100 protein highlights the monotonous population of neoplastic Schwann cells composing the tumor; supporting the diagnosis of schwannoma.