Recurrent schwannomatosis with mosaic SMARCB1 loss: A case report

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Abstract. Schwannomatosis is a non-cancerous disorder causing peripheral nerve sheath tumors (schwannomas), often leading to chronic pain. It is linked to loss of SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily B member 1 (*SMARCB1)* or leucine zipper-transcription regulator 1 *(LTZR1)* gene function, though some patients may initially show minor mutations or no clinical signs, resulting in misdiagnosis, missed assessments, increased recurrence risk, unawareness of malignancy and overlooked genetic counseling during pregnancy. The present study reports a patient with a sporadic synonymous mutation in the *SMARCB1* gene [SNP *c.1032 C>T (p.Gly344Gly {GGC>GGT})* in exon 8]. This patient, a 53-year-old female with an 8-year history of schwannomatosis, presented to the neurosurgical department for recurrent tumor removal. Tumor tissue was analyzed using immunohistochemistry, hematoxylin and eosin staining, and enzyme-linked immunosorbent assay. Initially, the clinical impact of the *SMARCB1* mutation on schwannomatosis was unclear. However, resected schwannomas showed 10-60% mosaic loss of nuclear *SMARCB1* protein, with protein assays confirming low *SMARCB1* levels, particularly in the distal thigh schwannoma. This case highlights the tumorigenic potential of *SMARCB1* single nucleotide polymorphisms, emphasizing the need for multimodal diagnosis, long-term follow-up, awareness of recurrence and malignancy, and timely surgical planning in schwannomatosis patients.

Introduction

Schwannomatosis is a rare neurocutaneous disorder characterized by the development of multiple schwannomas, benign tumors of the peripheral nerve sheath (1). The pathogenesis of schwannomatosis is complex and unclear, and it is often misdiagnosed with Neurofibromatosis type 2 (*NF2*) due to overlapping phenotypes (2). Schwannomatosis is distinct from *NF2*, which is characterized by bilateral vestibular schwannomas and is linked to mutations in the *NF2* gene (3). While schwannomas are the hallmark of schwannomatosis, the clinical presentation is highly variable, with symptoms ranging from mild to severe, including chronic pain and neurological deficits (4).

In recent years, studies have shown association between schwannomatosis and mutations in the *LZTR1* and *SMARCB1* genes (5). Both genes are involved in crucial cellular pathways, including tumor suppression and chromatin remodeling, and their disruption plays a role in tumor formation (6,7). Mutations in *SMARCB1* have been implicated less frequently than *LZTR1*, but their presence can suggest a more aggressive tumor phenotype, and in some cases, they are associated with the risk of malignant transformation (7-9). This understanding has enabled genetic testing not only for diagnostic confirmation of schwannomatosis but also for prognostic evaluation and personalized treatment plans (10).

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Abbreviations: NF2, neurofibromatosis type 2; *LZTR1*, leucine zipper-transcription regulator 1; *SMARCB1*, SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily B member 1; SNP, single nucleotide polymorphism; MRI, magnetic resonance imaging; H&E, hematoxylin and eosin; IHC, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay; CES, clinical exome sequencing; NGS, next-generation sequencing; WES, whole exome sequencing

Key words: schwannomatosis, SMARCB1, single nucleotide polymorphism, recurrence, case report

Intradural, extramedullary schwannomas are rare, accounting for approximately 2% of all spinal tumors (11). Here, we present the rare case of a patient with recurrent schwannomas located at the cauda equina and distal thigh, with mosaic loss of *SMARCB1* protein in the tumor cells revealed on immunohistochemistry. In addition to the rare location of this schwannoma, the mosaic loss of *SMARCB1* suggests a potential genetic alteration that may influence tumor formation, though this mutation is not yet fully understood in the context of schwannomatosis. This finding reinforces the complexity in the genetic mechanisms underlying schwannoma development and warrants further surveillance. Additionally, the multifocal nature and recurrence of schwannomatosis in this case highlights the importance of continued follow-up and comprehensive management for neuropathic pain and quality of life improvements.

Case presentation

A 53-year-old white female with a history of schwannomatosis diagnosis at 44 years-old presented to the clinic in 2021 with increasing symptoms of neurogenic claudication. The patient had undergone multiple nerve sheath tumor resections in the past with the first being of the cauda equina in 2013 and subsequently of the left axilla, right thigh, and left ankle. At the time, pathology supported schwannoma diagnosis of these tumor resections (Fig. 1). She had five cafe-au-lait macules and no family history with features or symptoms suggestive of neurocutaneous disease.

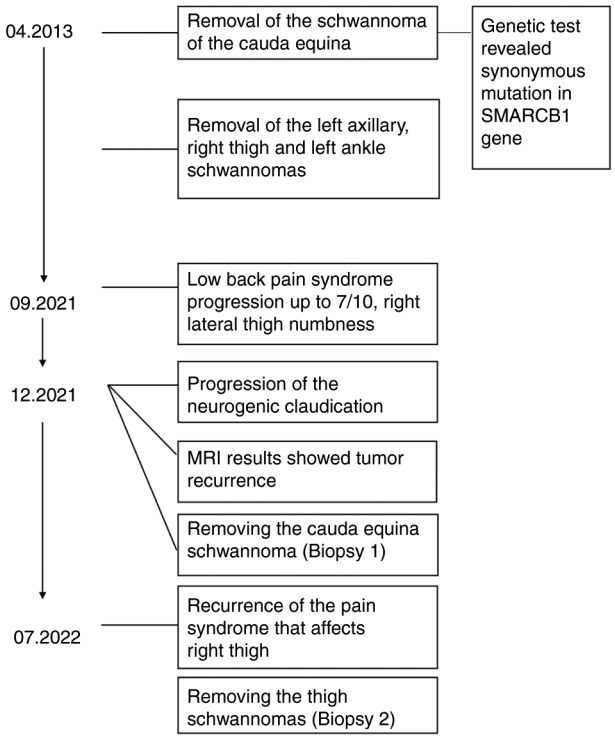

Figure 1. Timeline of case. This figure shows the timeline of the case in reference to the recurrent schwannomatosis removal.

Contrast magnetic resonance imaging (MRI) of the lumbar spine revealed an intradural extramedullary mass measuring approximately 11x11x24 mm at the L2-L3 level causing significant compression of the cauda equina nerve roots (Fig. 2A). A L1-L3 laminectomy was performed for resection of the intradural mass. Due to the patient's previous L2-L4 laminoplasty and tumor resection at the cauda equina in 2013, the procedure was complicated by scarring of the dorsal nerve roots and dura adherence but concluded with successful total resection. Pathology confirmed the masses as schwannomatosis. Proceeding surgery, the patient's recovery was without complications with no leaking from the incision, foley removed two days post-surgery with passed voiding trial, and pain was controlled. While recovering in the hospital, the patient was given acetaminophen (325 mg, oral) for pain, buspirone (10 mg, oral) for generalized anxiety, and gabapentin (300 mg, oral) for nerve-associated pain.

The patient returned home with family three days after surgery with no prescribed discharge medications. At discharge, the patient had bilateral thigh numbness and significant right lower extremity weakness. At the one-month post-operation appointment, the patient presented with no fever, no infection, well healed incision site. Seven months after the surgery, she regained significant function in her right lower extremity. At this appointment, the patient presented again with burning pain in her distal thigh.

Following this appointment, in 2022, subsequent MRI of the femur revealed enhancing lesions in the distal thigh in proximity to the right sciatic and right common peroneal nerve (Fig. 2B). The pain was determined to be caused by these masses found in the distal thigh in proximity to the right sciatic and right common peroneal nerve. After discussion with neurosurgery, the lesions in the distal thigh illustrated by MRI of the femur were removed with blunt dissection. Pathology confirmed the masses as schwannomatosis. The patient returned home the day of surgery with no complications. Tissue samples from both surgeries, laminectomy and distal thigh dissection, as well as control nerve samples from the ulnar nerve from a consenting patient with no genetic changes were sent for genetic sequencing, histopathological examination, and *SMARCB1* protein level quantification.

Comprehensive germline genetic analysis was conducted of the tissue using whole exome sequencing (WES) and clinical exome sequencing (CES) with Next-generation sequencing (NGS) technology, including all genes associated with schwannomatosis, *NF2*, and *LZTR1* (Table I). The analysis did not identify any pathological variants (PVs) or other gene mutations in *NF2*, and *LZTR1*. Although, a single nucleotide polymorphism (SNP) *c.1032 C>T [p.Gly344Gly (GGC>GGT)]* in exon 8 of the *SMARCB1* gene was identified as a likely benign variant of unknown significance.

H&E staining of both samples displayed a prominent myxoid background with the extensive deposition of stromal mucin, supporting the pathological diagnosis of schwannoma (Fig. 3A). The histologic sections showed an encapsulated tumor made up of spindle cells with a bland appearance, arranged in short bundles. The tumor exhibited areas with dense cellularity and nuclear palisading (Antoni A) alongside regions that were hypocellular (Antoni B). No histologic features of malignancy were identified.

IHC indicated positive strong expression of *S100* and *Sox10* (~78% and 90% respectively), markers commonly associated with schwannoma (Fig. 3A). ELISA demonstrated

Table I. Summary of variants detected by WES in schwannomatosis-associated genes.

Gene	Disease	Mode of inheritance	Variant	Classification
NF2	Schwannomatosis	Autosomal dominant	None detected	Normal/benign
LZTR1	Schwannomatosis	Autosomal dominant	None detected	Normal/benign
SMARCB1	Schwannomatosis	Autosomal dominant	c.1032 C>T	Variant of unknown significance/likely benign

NF2, neurofibromatosis type 2; *LZTR1*, leucine zipper-transcription regulator 1; *SMARCB1*, SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily B member 1.

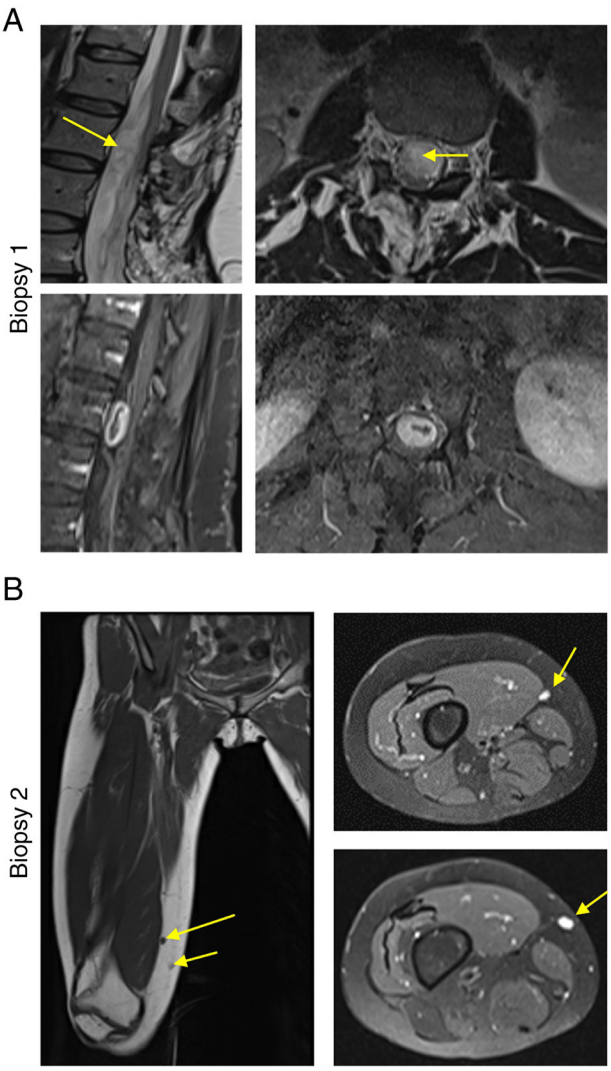

Figure 2. (A) Cauda equina schwannoma: Sagittal and Axial T2W images show an oblong lesion, which showed central hypointensity (indicated by arrows) suggestive of a 'Target sign' (top). Sagittal and axial postcontrast T1W images with intradural extramedullary ring-form contrast enhancement (bottom). (B) Subcutaneous schwannomas of the distal thigh: T1W coronal image shows two hypointense lesions (indicated by arrows) (left). Postcontrast T1W axial images show two hyperintense lesions within soft tissue of the medial thigh (indicated by arrows) (right).

mosaic loss of nuclear *SMARCB1* protein was present in both samples ranging from 10 to 60% with significant loss of *SMARCB1* expression in the distal thigh sample. Additionally, ELISA indicated statistically significant lower concentrations of *SMARCB1* in both biopsies compared to the control nerve sample ($P<0.05$) (Fig. 3B).

Discussion

This case is an unusual presentation of recurrent schwannomas, mosaic loss of *SMARCB1*, and no identifiable direct genetic alteration that is pathogenic. The only identified alteration is *SMARCB1:c.1032C>T, p.Gly344Gly* which is a synonymous change and has been reported in ClinVar five times as a likely benign or benign variant (12). Based on NHLBI Exome Sequencing Project (phs000422.v1.p1), this mutation is not observed at any significant frequency with 6,500 individuals being of European and African ancestry. According to ACMG guidelines, this variant should be classified as a likely benign variant and not considered the cause of the patient's disease, whether it is of de novo or inherited origin (13). While no clear pathogenic SMARCB1 mutation was identified, the observed mosaic loss of SMARCB1 suggests a potential role in disease pathogenesis by impairing tumor suppressor mechanisms and deregulation of gene expression and cell cycle control.

While exact recurrence rates for spinal schwannomas can vary depending on the series, studies show spinal schwannoma recurs after initial surgery at a rate of 4-6% (14). Known risk factors include subtotal resection, tumor size and location, histopathology characteristics, and follow-up (15). The relationship between *SMARCB1* loss and schwannoma recurrence is complex. While *SMARCB1* loss is associated with the development of certain schwannomas, its role in recurrence is not entirely clear and needs further research to be fully understood. For instance, a study on epithelioid schwannomas discovered that while most tumors followed a benign clinical course, some with notable cytologic atypia showed recurrence or malignant transformation (16). Additional research on epithelioid malignant peripheral nerve sheath tumors, which can arise from pre-existing schwannomas, revealed that *SMARCB1* inactivation is a recurrent event (17).

This report illustrates that effective management of recurrent schwannomas hinges on early detection, regular monitoring, and a comprehensive, multidisciplinary approach even when genetic testing shows no clear mutative cause. Early detection of recurrence may allow for timely intervention, minimizing the need for extensive

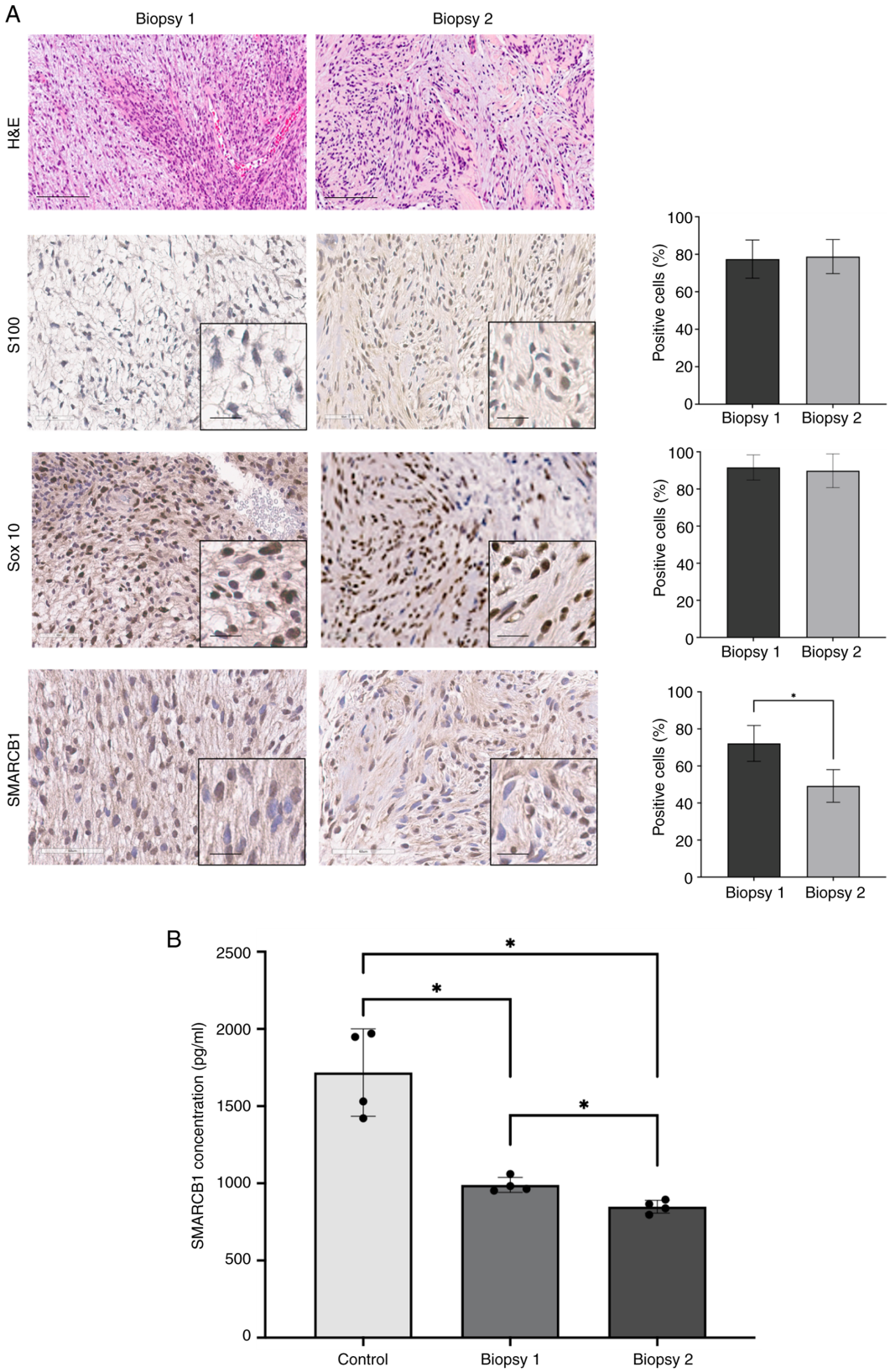

Figure 3. (A) (Top to bottom) High-power H&E-stained section images of removed schwannomas during first and second surgeries. The recurrent neoplasm, intradural mass attached to the cauda equina roots. Image showing spindle cell neoplasm with hypercellular Antoni A and myxoid hypocellular Antoni B areas. Blood vessels have thickened hyalinized walls. Nuclear palisading around fibrillary process (Verocay bodies). Scale bar, 100 μm. S100 immunohistochemistry and quantification demonstrating intense diffuse labeling of nuclei and cytoplasm of the tumor cells. Sox10 immunohistochemistry and quantification representing positive nuclear staining: Elongated nuclei, no mitotic figures. Immunohistochemical staining with SMARCB1 antibody. Mosaic nuclear staining for SMARCB1 protein in the cauda equina roots and distal thigh schwannomas with the c.1032 C>T mutation. There is notable statistical loss in SMARCB1 expression in the distal thigh schwannoma. Original scale bar, 60 μm. Magnified scale bar, 20 μm. (B) ELISA SMARCB1 Concentrations for Biopsy 1, Biopsy 2 from SMARCB1 mutation patient and the control nerve sample from the SMARCB1 wild-type patient. Samples were split into four different areas to conduct four replicates of the ELISA assay (n=4). *P<0.05 (one-way ANOVA; data are shown as means ± SEM). SEM, standard error of the mean; H&E, hematoxylin and eosin; SMARCB1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily B member 1.

treatment and preserving the patient's quality of life. Long term, regular follow-ups with physical assessments help in identifying new neurological symptoms, such as pain, weakness, or sensory deficits, which might indicate tumor progression. Monitoring also facilitates the stratification of tumors by risk and guides decisions about the urgency and type of intervention needed. By integrating surgical expertise, advanced imaging, pain management, and genetic counseling, clinicians can tailor individualized care plans that address both the immediate and long-term needs of patients with recurrent schwannomas.

Despite the comprehensive genetic analysis of WES and CES conducted in this report, a limitation is the possibility that *SMARCB1* pathogenic variants may escape detection. WES primarily captures exonic regions and may miss pathogenic variants in intronic regions, which could affect gene expression without being detected by standard exome sequencing approaches. There are also limitations of mosaicism detection, as WES has reduced sensitivity for low-frequency mosaic variants. Because of this limitation, promoter analysis was also not conducted in this study. Future investigations could incorporate tumor genetic testing to provide a more comprehensive understanding of potential somatic mutations and the promoters contributing to the disease.

In conclusion, in this case report, a patient with mosaic loss of *SMARCB1* protein exhibits recurrence of schwannomas impacting her quality of life. A better understanding of the role of *SMARCB1* loss in schwannomas and a multi-leveled approach to diagnosis and treatment may improve diagnostic accuracy, prognostication, and treatment strategies, offering hope for more personalized approaches to managing this challenging condition.

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Availability of data and materials

Exome sequencing was provided by GeneDx. GeneDx data cannot be shared publicly due to consent restrictions tied to clinical testing. Patients referred to GeneDx consent to deidentified, aggregate research use under HIPAA privacy protections. As such, patient-level exome sequencing files, which may be identifiable, cannot be shared without a HIPAA Business Associate Agreement or other legally required contract. Requestors must meet all HIPAA requirements for data access, use, disclosure and storage. Once all documentation is in place, patient-level data may be shared per the terms of the agreement. Deidentified aggregate data from this analysis are available upon request to GeneDx (support@genedx.com), with typical fulfillment within 60 days. Data was shared in accordance with patient consent guidelines to support improved clinical interpretation.

Authors' contributions

NMB and KL conceived the project. YL and MGY designed and performed most of the experiments. YL, MAL and MGY critically analyzed the data. MC handled patient materials. MST, YD, MAL and SK aided with the interpretation of data and critically read the manuscript. Manuscript drafting and figure preparation were performed by YL, MAL and MGY. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Emory University IRB (approval no. STUDY00002544). Informed consent was obtained from the patient in accordance with the ethical principles of the Declaration of Helsinki. The patient has provided written consent for the publication of the data.

Patient consent for publication

Written consent was obtained from the patient for publication of clinical data and images.

Competing interests

The authors declare that they have no competing interests.

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