

CASE REPORT

Hereditary intraspinal schwannomatosis with SMARCB1 gene mutation: A case report

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Abstract

Background: Schwannomatosis is the third subtype of neurofibromatosis. Schwannomatosis, particularly the familial variant, is uncommon. Recently, germline mutations of the SMARCB1 gene have been found to cause schwannomatosis. In this report, we describe a case of familial inherited intraspinal schwannomatosis. Postoperative pathology indicated a schwannoma. The results of gene testing showed that the SMARCB1 gene had a spliced mutation.

Case description: A patient with a rare case of familial intraluminal schwannomatosis was admitted to our hospital. Peripheral blood gene testing was performed on the patient and her son, and a splice mutation of the SMARCB1 gene located at C. 1118+1G>A on intron 8 was identified.

Conclusions: Schwannomatosis is an incomplete dominant autosomal dominant genetic disorder. The structural and functional abnormalities of proteins caused by mutations in the SMARCB1 gene may be the molecular basis for familial schwannomatosis.

KEYWORDS

family inheritance, schwannomatosis, SMARCB1

1 | BACKGROUND

Schwannomatosis is the third subtype of neurofibromatosis,^{1,2} and accounts for less than 1% of all neurofibromatosis.³ Schwannomatosis is rarely observed in the clinic, with an annual incidence of 0.58 per 1 million cases.⁴ The pathogenesis, diagnosis, and treatment of schwannomatosis are far more complex than those for a single schwannoma. In addition, schwannomatosis is often misdiagnosed clinically as neurofibromatosis type 2 (NF2) due to a lack of systematic understanding of the disease and phenotypic overlap with NF2.⁵ Schwannomatosis is a unique syndrome characterized by multiple peripheral nerve schwannomas

that are mostly benign and originate from the Schwann sheath of nerve roots. Schwannomas typically grow slowly, and most often affect peripheral and spinal nerves. The prognosis for patients with schwannomatosis is typically good following total resection. Schwannomatosis can be sporadic or familial,⁶ and is characterized by the development of multiple schwannomas in the absence of bilateral vestibular schwannomas. Most schwannomas occur as isolated lesions, but cases of schwannomatosis with multiple lesions can occur. Schwannomatosis is often familial, and is clinically significant. Here, we report a rare case of SMARCB1 gene germline mutation associated with familial schwannomatosis with radiographically confirmed meningioma.

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2 | CASE DESCRIPTION

A 59-year-old female presented with needle-like pain in her waist that began 7 months prior to evaluation and was accompanied by numbness in both lower limbs. The patient took oral ibuprofen for pain relief at each onset. The patient first came to our hospital in response to poor control of symptoms by oral ibuprofen. Physical examination showed clear consciousness, normal vision and visual field, no headache or dizziness, grade 4 muscle strength in the right lower limb, grade 5 muscle strength in the left lower limb, muscle strength of both upper limbs was normal, normal muscle tone, normal pain sensation in all extremities, positive straight leg lift test (+), positive four-word test (+), negative bilateral Hoffmann's sign (-), negative bilateral Babinski's sign (-), and no subcutaneous nodules. The patient had a surgical history of thoracic spinal schwannoma 2 years prior. She had type 2 diabetes for more than 5 years and hypertension for more than 10 years. She took hypoglycemic drugs and antihypertensive drugs orally regularly, and her blood glucose and blood pressure were well controlled. Her preoperative MRI examination of the thoracic and lumbar vertebrae showed the following at the posterior edge of L3: circular and slightly shorter T1 and long T2 signals, about 1.5×0.7 cm, in the spinal canal of the extramedullary and subdural regions, with a clear boundary and obvious enhancement following enhancement, with unenhanced areas within the circular regions. Multiple extramedullary subdural nodules were present in the posterior spinal canal of the L1-L3 vertebral body and the T4/5 vertebral space showed long T1 and short T2 signals, which were significantly enhanced following enhancement (Figure 1A). Cranial MRI showed irregular T1 and T2 signals about 1.6×2.5 cm in size in the cerebello-pontine angle area of the left dorsum sella, with clear boundaries and obvious enhancement. These signals were connected to the dorsum sella with a broad base, and showed a meningeal tail sign (Figure 1B). After complete preoperative examination and elimination of surgical contraindications, we selected the T12-L4 spinous process level for a longitudinal posterior midline incision.

Layer by layer separation was performed to expose the surgical field of vision, and five tumors of different sizes that were fleshy red with general blood supply were observed. The tumor tissues were carefully removed from the nerves one by one with extra attention to the protection of the nerves (Figure 2). Following tumor resection, hemostasis was achieved and the incision was sutured layer by layer. After surgery, the patient experienced significant relief of symptoms, with only mild pain during lower extremity movement, which was largely resolved at discharge. Postoperative MRI of the lumbar spine showed postoperative changes at the T12-L3 levels without significant stenosis or abnormal signals (Figure 3A). Pathology indicated that the excised tumors were schwannomas (Figure 3B). Since the patient's son also had a history of schwannoma (confirmed by pathology), peripheral blood gene tests were performed on the patient and her son. The results of genetic testing indicated that a splice mutation of the SMARCB1 gene at C. 1118+1G>A on intron 8 was present in both individuals (Figure 4). No possible pathogenic mutation sites were found in neurofibromatosis-related genes such as NF1 and NF2. Since the patient was treated for low back pain at this time, only tumor tissue in the spinal canal was removed to relieve the clinical symptoms, and the suspected meningioma in the intracranial region was left for future treatment.

3 | DISCUSSION

Schwannomatosis was first identified as neurofibromatosis type 3⁷ in 1997. It is often familial in nature and results from autosomal incomplete dominant inheritance. The most common genetic alteration is a mutation of the SMARCB1 gene or LZTR1 gene on chromosome 22q11.2,⁶ with less than 20% of cases originating from the affected parent. Schwannomatosis associated with LZTR1 and SMARCB1 accounted for about 30% and 10% of cases, respectively.^{8,9} The pathogenesis of schwannomatosis remains unclear. In recent years, many studies have suggested that gene mutations may play a key role in

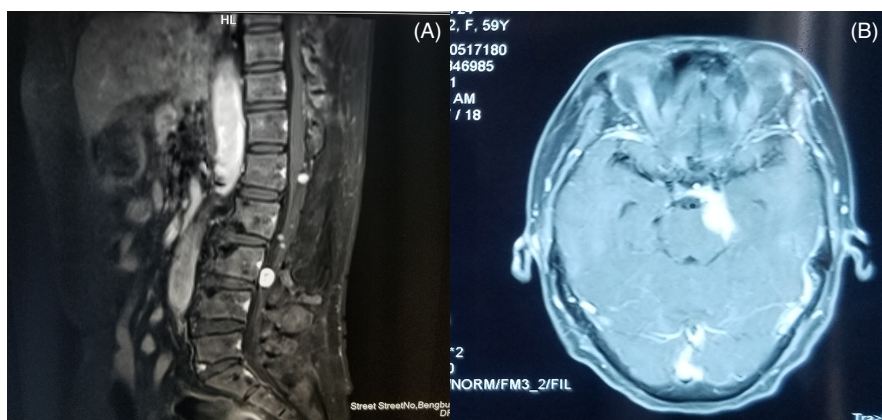


FIGURE 1 (A): Multiple long T1 and short T2 signals of extramedullary subdural nodules were observed in the posterior spinal canal of L1-3 vertebral body and T4/5 vertebral space. These areas were significantly enhanced following enhancement. (B): Head MRI showed irregular T1 and T2 signals approximately 1.6×2.5 cm in size in the cerebello-pontine angle area of the left dorsum sella, with clear boundaries and obvious enhancement, and connected with the sellar dorsum with a broad base, and meningeal tail sign

the onset and development of schwannomatosis. However, the gene mutations of this disease do not have a certain regularity, and most reports suggest that abnormal expression of the SMARCB1 and LZTR1 genes is strongly correlated with the onset and development of the disease.¹⁰⁻¹² Mutations of SMARCB1 are also associated with

meningioma, which occurs in about 5% of schwannomas, and has been reported only in SMARCB1-related schwannomas.^{4,8} However, the role of each gene in the pathogenesis of schwannomatosis, and whether each gene promotes or inhibits this pathogenesis, is unclear. Schwannomatosis is often clinically diagnosed as NF2 because the phenotype of schwannomatosis overlaps with NF2 and the etiology and pathogenesis of schwannomatosis are poorly understood. Based on current knowledge, the National Institutes of Health (NIH) has proposed the following new criteria for diagnosis²:

Molecular Diagnosis:

- Two or more pathologically confirmed schwannomas or meningiomas and genetic studies of at least two tumors with loss of heterozygosity (LOH) for chromosome 22 and two different NF2 mutations. If there is a common SMARCB1 mutation, it is defined as SMARCB1-associated schwannomatosis.
- One pathologically confirmed schwannoma or meningioma AND a germline SMARCB1 pathogenic mutation

Clinical Diagnosis:

- Two or more non-intradermal schwannomas, one with pathological confirmation, including no bilateral vestibular schwannoma as determined using high-quality MRI (detailed study of the internal auditory canal with slices no more than 3-mm thick). Some patients with NF-2 will be included in this diagnosis at a young

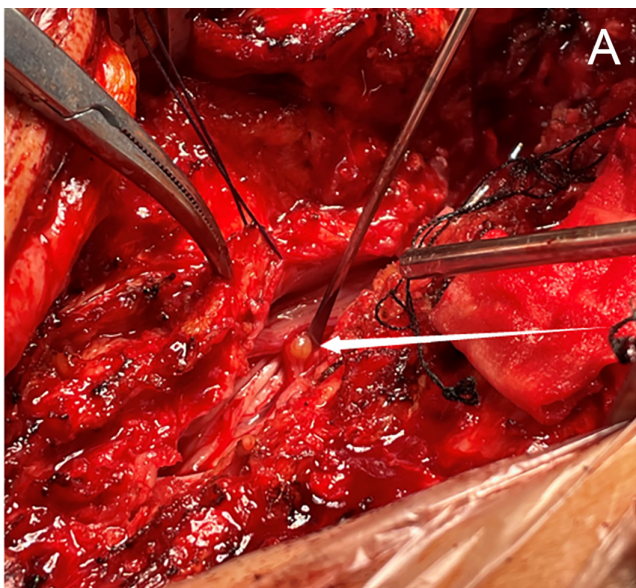


FIGURE 2 The arrow indicates the schwannoma tissue isolated during surgery

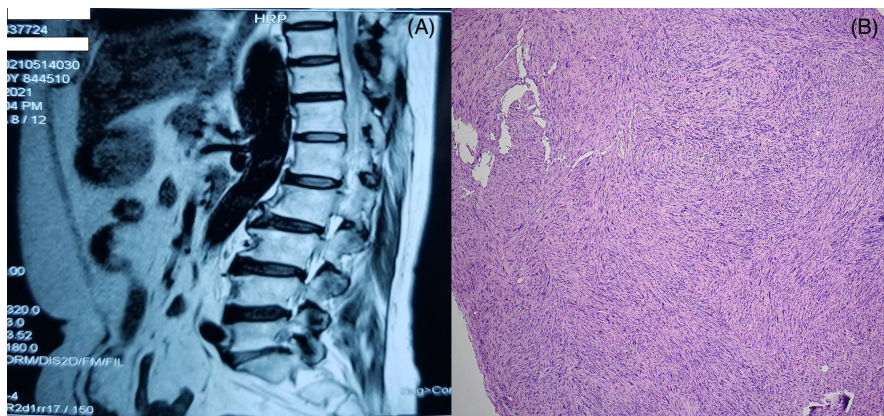


FIGURE 3 (A): The T12-L3 levels were changed following lumbar surgery, and no obvious stenosis or abnormal signals were observed. (B): Schwannoma pathological section, HE staining, 100x magnification, increased spindle cells

SMARCB1:NM_003073.5:intron8:c.1118+1G>A:

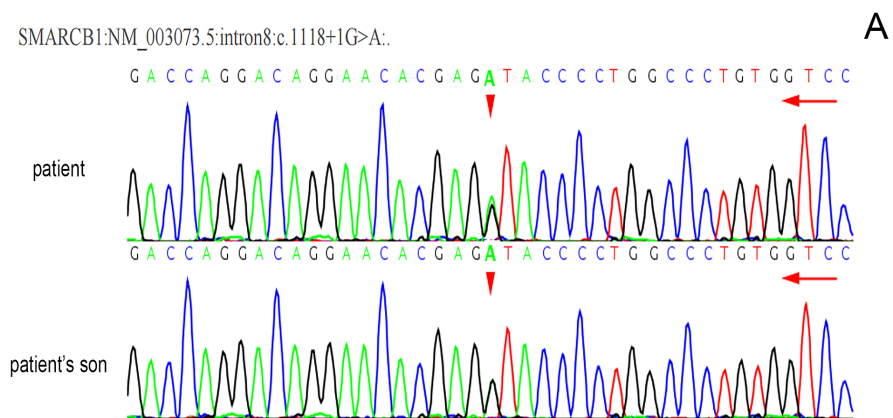


FIGURE 4 The mutation location, C. 1118+1G>A on intron 8, from the genetic tests of the patient and her son

age and some patients with schwannomatosis patients have been reported to have unilateral vestibular schwannomas or multiple meningiomas.

- One pathologically confirmed schwannoma or intracranial meningioma and an affected first-degree relative.
- Consider diagnosis if there are two or more non-intradermal tumors, but none have been pathologically confirmed to be a schwannoma. Chronic pain in association with the tumor(s) increases the likelihood of schwannomatosis.

The following do not meet the diagnostic criteria for schwannomatosis:

- Germline pathogenic NF2 mutation
- Fulfill diagnostic criteria for NF2
- First-degree relative with NF2
- Schwannomas in previous field of radiation therapy only.²

The clinical manifestation of schwannomatosis is often pain caused by tumor compression of peripheral nerves. Diagnosis often depends on histopathology and molecular science, and surgical resection of tumor tissue is the only treatment option. Our patient had pathologically confirmed schwannoma, and both she and her son had a SMARCB1 gene mutation, thus meeting the diagnostic criteria for the familial inheritance of intraspinal schwannomatosis with SMARCB1 gene mutation.

The SMARCB1 gene is located at 22q11.2 and contains nine exons in the transcriptional region NM_003073.4. This gene encodes the SMARCB1 protein, which acts as a tumor suppressor.^{2,9} Studies have shown that SMARCB1 is a subunit of the SWI/SNF complex, which is an ATP-dependent chromatin remodeling complex that exerts anti-cancer activity by regulating the cell cycle and inducing senescence.^{5,13} The SMARCB1 gene was first reported as a gene associated with schwannomatosis in 2007.² The relationship between a germline mutation of the SMARCB1 gene and familial schwannomatosis has attracted increasing attention. In 2015, an Asian family with schwannomatosis and a SMARCB1 gene mutation was reported for the first time in Japan.¹⁴ Studies have found that the main mutations detected in patients with schwannomatosis are missense mutations and splicing-site mutations. And different mutation sites have been reported.^{15,16} Schwannoma-associated SMARCB1 mutations are commonly located at the 5' or 3' end of the gene, including the 3'-untranslated region where the most common pathogenic variants are located, including c.*82C>T.^{9,17} An epidemiological study of schwannomatosis from the University of Manchester in the United Kingdom reported SMARCB1 gene mutations in approximately 45% of patients with familial schwannomatosis and 7% of patients with sporadic schwannomatosis.¹¹ Somatic SMARCB1 mutations have also been found in sporadic rhabdomyomas, epithelioid sarcomas and meningiomas, but are more likely to occur in familial schwannomatosis. Irene Paganini et al. found that splicing mutations lead to changes in SMARCB1 protein through genetic analysis.¹⁵ In this familial case of schwannomatosis, both

the patient and her son had germline mutations of the SMARCB1, and both were splicing-site mutations (C.1118 +1G>A). We believe that splicing mutation at this site results in deletion of the carboxyl terminus of amino acid 44 of SMARCB1 protein, but we did not further investigate the effect of this mutation on SMARCB1 protein function. Studies have shown that in schwannomatosis, mutations in the germline SMARCB1 encode proteins with some residual functions,¹² and the structural and functional abnormalities of proteins caused by mutations may be the molecular basis of schwannomatosis. However, there are few reports on splicing mutations at this site. Studies have shown that concurrent meningioma occurs in approximately 5% of schwannomas and is only reported in SMARCB1-related schwannomas. In this case, the head MRI showed a possible meningioma in the cerebello-pontine angle area, which is very rare. Schwannomatosis is an inherited disease, so screening for genetic mutations in patients with a family history of schwannomatosis is necessary.

4 | CONCLUSION

Schwannomatosis is an incomplete autosomal dominant genetic disorder. The structural and functional abnormalities of proteins caused by mutations in the SMARCB1 gene may be the molecular basis for schwannomatosis in the family described in this case study. Schwannomatosis is associated with high rates of relapse and malignant transformation, which often affects patient quality of life. Therefore, it is particularly important to study the pathogenesis and etiology of schwannomatosis.

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Not applicable.

CONFLICTS OF INTERESTS

The authors state that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Y.L., L-L.C. and D-Q.S. conceived the framework of this article and collected the data. Y.L., B-B.Z., and S.X. drafted the manuscript. Y.L., L-L.C., and S.X. interpreted and analyzed the data. X-L.Z. and Z-Q.J. revised the manuscript. All authors read and approved the final version of the manuscript.

CONSENT FOR PUBLICATION

Written informed consent for publication of this case report was obtained from the patient.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, Zhiqian Jiang.

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