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Malignant progression of a peripheral nerve sheath tumor in the setting of rhabdoid tumor predisposition syndrome

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Abstract

Malignant progression of a benign or low-grade tumor in individuals with germline alteration of *SMARCB1* gene is not well characterized. In a family in which 2 carrier children had germline *SMARCB1* mutations and atypical teratoid rhabdoid tumor, we report malignant progression of a nerve sheath tumor over a 7-year period in an affected adult family member. Prompt identification of the germline *SMARCB1* alteration and the resultant rhabdoid tumor predisposition syndrome can help guide genetic counseling and surveillance in affected family members.

Keywords

rhabdoid tumor predisposition syndrome; malignant progression; peripheral nerve sheath tumor; NRAS mutation

INTRODUCTION

Somatic alterations of the *SMARCB1* gene on chromosome 22q11.2, a core component of the SWI/SNF family of chromatin remodeling complexes,^{1,2} occur in various cancers, including atypical teratoid rhabdoid tumor (ATRT).^{1,3–6} About a third of the patients with rhabdoid tumors (RTs) have heterozygous *SMARCB1* germline alteration, leading to rhabdoid tumor predisposition syndrome type I (RTPS1) and increased risk of multifocal

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and/or familial RTs.⁷⁻⁹ Germline *SMARCB1* alterations are also associated with familial schwannomatosis¹⁰ and more aggressive malignancies (e.g., soft tissue or nerve sheath sarcomas).¹¹⁻¹³ We report ATRT in two children and a peripheral nerve sheath tumor in an adult of a family with a germline *SMARCB1* mutation. The family provided informed consent for the report, and the study was approved by the institutional review board of St. Jude Children's Research Hospital.

CASE PRESENTATION

A 17-month-old female presented with a 1-week history of right extremity weakness and refusal to walk. Brain magnetic resonance imaging (MRI) demonstrated a large left-sided supratentorial mass. There was family history of colon cancer in a paternal uncle, unspecified female reproductive cancer in a maternal great aunt, and a brain tumor of unknown type at 2 years of age on the maternal side. She underwent tumor resection, and histology was confirmed as ATRT. There was no evidence of cranio-spinal metastasis or synchronous renal RT. She was treated on our institutional ATRT protocol, comprising 4 cycles of multi-agent chemotherapy followed by 54 Gy of focal proton beam radiotherapy. Germline testing of peripheral blood in a commercial lab revealed a pathogenic heterozygous splicing mutation in exon 7 of *SMARCB1* (c.986G>C; RefSeq: NM_003073.3).

Screening of parents confirmed that the 33-year-old mother harbored the same *SMARCB1* mutation. Mother's history revealed chronic neuropathic pain in the right upper extremity that was associated with gradual weakness of the arm over the past 7 years. Imaging of the affected extremity revealed enlargement of right brachial plexuses and of multiple lower cranial and thoracic nerves (Fig. 1A). Core needle biopsy of the brachial plexus lesion performed at the onset of symptoms had been interpreted as inflammatory neuropathy. Repeat imaging studies obtained currently, 7 years after initial presentation, revealed significant progression in the lesion involving brachial plexuses, with extension into thorax and cervical spine neural foramina (Fig. 1B). Repeat biopsy showed fascicles of monomorphic spindle cells with elongated hyperchromatic nuclei (Fig. 1D) with mitotic activity (5 mitotic figures per 10 high-power fields), accentuated perivascular cellularity, punctate foci of necrosis, and complete absence of S-100 protein (Fig. 1F). There was complete loss of *SMARCB1*/INI-1 expression (Fig. 1G) and histone H3K27 trimethylation in tumor cells. Immunohistochemical analysis with a broad panel of markers excluded several entities considered in differential diagnosis, such as solitary fibrous tumor, synovial sarcoma, myofibroblastic sarcoma, and rhabdomyosarcoma (Supplemental Table S1).^{14,15} Review of the initial needle biopsy taken 7 years earlier showed hypocellular proliferation of bland-looking spindle cells with wavy tapering nuclei, no mitotic activity (Fig. 1C), S-100 expression (Fig. 1E), and mosaic *SMARCB1*/INI-1 expression. Fluorescence in situ hybridization analyses of original and subsequent biopsy samples showed hemizygous *SMARCB1* deletion in approximately 50% of evaluable nuclei (Fig. 1H). These findings indicated a benign/low-grade peripheral nerve sheath tumor in the initial needle biopsy and progression to intermediate-grade malignant peripheral nerve sheath tumor (MPNST) in the subsequent biopsy. Next-generation sequencing and copy number analysis of the tumor at progression by Foundation One Medicine revealed the germline *SMARCB1* alteration, a

KRAS G12R mutation, and an *EWSR1–RHBDD3* fusion with no NF-1 and NF-2 gene alterations. The mother received multiple sarcoma-directed chemotherapy regimens, including doxorubicin, ifosfamide, gemcitabine, docetaxel, and pazopanib, and radiation therapy, but ultimately underwent palliative amputation of her right arm due to significant pain and lack of arm mobility. She continues to have intrathoracic disease and follows up with her oncologist since the diagnosis of sarcoma 3 years ago.

Subsequent evaluation of our patient's maternal aunt and her child (patient's first cousin) revealed the same germline *SMARCB1* mutation (Fig. 2). Screening brain MRI in the patient's first cousin revealed an ATRT who has currently completed therapy for the tumor.

DISCUSSION

MPNST occurs at increased frequency in individuals with neurofibromatosis type 1 (NF-1)¹³ but is rarely associated with other inheritable diseases, with Evans and colleagues reporting only 3 cases of co-occurrence of MPNST and schwannomatosis.¹³ Interestingly, 2 of them occurred in a family with proven *SMARCB1* mutations. Germline *SMARCB1* alterations are detected in patients with RTPS1 and some patients with familial schwannomatosis.^{9,10,16} In families with RTPS, some members develop a benign tumor-like schwannoma whereas others develop more malignant tumors (e.g., sarcomas or RTs), which highlights incomplete penetrance and variable expressivity of this germline alteration and the phenotypic overlap between RTPS and schwannomatosis.¹⁷ A *SMARCB1* mutation carrier may thus pass through the developmental window wherein RT risk is highest, without developing RT, but later develop other malignancies. This is likely due to the timing of *SMARCB1* loss. Vitte and colleagues demonstrated that *SMARCB1* loss in early neural crest cells of mice results in cranial nerve tumors resembling human rhabdoid tumors, whereas its loss at later developmental stages along with biallelic loss of *NF-2* results in schwannomas.¹⁸

Germline *SMARCB1* alterations associated with RT are typically truncating, spare exons 1, 8, and 9, and include whole-gene deletions, nonsense mutations, and intragenic deletions/duplications, leading to complete loss of protein expression in the tumor. Approximately 10% of the alterations are splice site mutations.^{3,19} In contrast, non-truncating splice site and missense mutations predominantly affecting exon 1 and the 3' untranslated region occur in familial schwannomatosis.^{19,20} This results in production of a partially functioning *SMARCB1* protein in patients with schwannomatosis. Immunohistochemically, this genetic difference manifests as complete loss of tumor nuclear *SMARCB1*/INI-1 expression in RT versus a mosaic staining pattern in schwannomatosis.^{1,17,21} Complete loss of *SMARCB1* expression in MPNST in the presence of a mosaic hemizygous *SMARCB1* loss in the mother of our index case is intriguing. Hulsebos and colleagues also observed complete loss of tumor *SMARCB1* expression in the presence of a germline *SMARCB1* alteration and partial tumor LOH of *SMARCB1* in their patient with papillary renal cell carcinoma.²² The splice donor site affected by germline mutation in the family we report is also reported in several other families with ATRT, with presumably the same pathogenic consequence of exon 7 skipping during mRNA transcription. These families include a patient with ATRT with germline mutation (c.986+2T>A), with no details of clinical and family history;¹⁹ a

family in which 3 of 4 children had ATRT and the unaffected father had a c.986+1G>C mutation;¹⁶ and a family with posterior fossa brain tumors and an exon 7 donor splice site mutation.²³ In the last 2 families, the germline mutation was inherited from an unaffected parent.

Loss of histone H3K27 trimethylation is highly specific for MPNST, distinguishes it from other closely related and sometimes histologically indistinguishable spindle cell neoplasms,²⁴ and indicates progression of MPNST to higher-grade tumors.^{24,25} The tumor Ras-MAPK kinase pathway is activated in patients with MPNST.²⁶ Activating Ras mutations are oncogenic in several cancers, and a recent study showed that aurora kinase A, a repressed target of *SMARCB1*, interacts with *H-RAS* to augment Ras-MAPK signaling.²⁷ Whether a similar potentiation of Ras signaling in presence of *KRAS* G12R by aurora kinase A contributed to malignant progression in the mother remains undetermined. Although fusions involving *EWSR1* can be oncogenic in Ewing sarcoma, the *EWSR1-RHBDD3* fusion is not well characterized. Interestingly both genes are located on chromosome 22 and share a common promoter region.²⁸

Although there are reports of MPNST developing in the presence of germline *SMARCB1* alterations,^{13,29} we found no reported cases of conventional spindle cell variants of MPNST in family members of individuals with RTPS. Biopsy of the brachial lesion in the mother of our index case, interpreted earlier as inflammatory neuropathy, was consistent with a benign-looking nerve sheath tumor. However, because of small sample size, we could not confirm whether it represented a low-grade nerve sheath tumor, a neurofibroma, or the Antoni B zone of a schwannoma. After a prolonged period of stable symptoms, sudden deterioration in her clinical condition indicated more aggressive disease, prompting a repeat biopsy. Histopathological examination revealed a change in cellular features that was compatible with a more aggressive-appearing sarcoma. Notably, change in the tumor's clinical behavior points strongly to malignant progression of a benign/low-grade lesion. Foulkes and colleagues recently provided guidelines for cancer screening in RTPS.³⁰ Worsening symptoms, coupled with detection of a germline alteration in the mother, prompted her to seek immediate medical attention for neurological problems. Moreover, MRI screening of our patient's cousin revealed an ATRT that was successfully treated, which emphasizes the importance of surveillance in these patients.

In conclusion, our report highlights the important role of pediatric oncologists in early referral of a child with ATRT and the family for genetic counselling to identify germline *SMARCB1* alterations, prompt screening for cancers and close surveillance. Affected families and medical providers need to be vigilant about the possible risk of malignant progression of a benign tumor in the setting of RTPS, further reinforcing the need for continued surveillance in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ATRT	Atypical teratoid rhabdoid tumor
MRI	Magnetic resonance imaging
MPNST	Malignant peripheral nerve sheath tumor
NF-1	Neurofibromatosis type 1
NF-2	Neurofibromatosis type 2
RT	Rhabdoid tumor
RTPS	Rhabdoid tumor predisposition syndrome
SMA	Smooth muscle actin
HHV8	Human herpes virus-8

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Figure 1. Imaging and histologic analysis of the tumor in the mother of the index case (A) MR axial T1-weighted image showing peripheral nerve enlargement of right brachial plexuses. (B) Repeat MR axial T1-weighted image taken 7 years after initial presentation showing a more aggressive-appearing lesion involving the right brachial plexuses (black arrow), with extension into the thorax (white arrow). (C) Hematoxylin and eosin–stained (H&E, 20×) section of the brachial plexus biopsy showing bland-looking spindle cells with wavy or buckled nuclei, suggestive of a benign/low-grade nerve sheath tumor. (D) H&E (20×) section of an intermediate-grade MPNST showing cellular proliferation of monomorphic spindle cells with a fascicular growth pattern and a hemangiopericytoma-like vascular pattern. (E) Immunostaining for S-100 protein in the initial biopsy. (F) Absence of immunostaining for S-100 at progression. (G) Immunohistochemical staining for SMARCB1/INI-1 in the MPNST showing complete loss of nuclear SMARCB1/INI-1 expression. Endothelial cells were used as positive internal controls. (H) Interphase fluorescence in situ hybridization for *SMARCB1* demonstrating 22q monosomy.

Figure 2.

Pedigree of the family of the index case. + SMARCB1, positive for familial *SMARCB1* mutation c.986G>C; ATRT, atypical teratoid/rhabdoid tumor; d, age at death; dx, age at diagnosis; MPNST, malignant peripheral nerve sheath tumor; NOS, not otherwise specified; NT, not tested for *SMARCB1* mutation; mets, metastases; mos, months; yrs, years.