Gonadal Mosaicism in Rhabdoid Tumor Predisposition Syndrome

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Keywords

Rhabdoid tumor predisposition syndrome ; gonadal mosaicism.

Abstract

Rhabdoid tumor (RT) is a malignant tumor occurring in children with a peak incidence between 1-4 years of age. The tumor exhibits diverse subtypes: atypical teratoid rhabdoid tumor (ATRT), malignant rhabdoid tumors in the kidney (MRTK) and extrarenal tumors (MRT). These malignancies are associated with a pathogenic variant in *SMARCB1* (98%) or *SMARCA4* (2%). Within 25-35% there is a germline pathogenic variant leading to rhabdoid tumor predisposition syndrome (RTPS). These variants can be inherited in an autosomal dominant mode, but most occur de novo. Even with a multimodal treatment the prognosis is poor. We report on a family with 2 siblings diagnosed with RT due to a germline nonsense pathogenic variant in *SMARCB1* caused by gonadal mosaicism. This germline variant was found in the 9-month-old brother who presented with metastatic MRTK and was absent in the parents. However familial recurrence of an RT occurred when a newborn sister presented with an ATRT. Both patients died from the disease. SNP haplotyping identified maternal gonadal mosaicism. Only seven families affected by RTPS due to gonadal mosaicism have been reported in the literature. The current new and more extensive genetic tests will probably identify more families with RTPS due to gonadal mosaicism. However, most germline pathogenic variants in children of healthy parents arise de novo, making it challenging to predict the risk of RT development in siblings. Therefore, extensive genetic testing in families with a child affected by RTPS is necessary to rule out gonadal mosaicism and to more accurately predict the possible recurrence risk of RT in siblings.

Introduction

Rhabdoid tumor (RT) is a rare malignant tumor that occurs mostly in young children and infants with a peak incidence between 1 and 4 years (1). These RTs are divided into different groups according to their location. The most frequent is an atypical teratoid rhabdoid tumor (ATRT) which occurs in the central nervous system (65%). Furthermore, there are malignant RTs in the kidney (MRTK) (9%) and in extrarenal tissues (MRT) (26%). The extrarenal sites encompass the head and neck, liver, lungs, and almost all soft tissues and viscera (2). In more than 50% of the cases, metastases are present at diagnosis, the most frequent sites being the lungs, liver, lymph nodes and brain (3). Approximately 10% of the tumors present as synchronous tumors (4).

In 98% of the RTs, immunohistochemistry shows loss of INI-1 protein expression due to a *SMARCB1* deletion or a pathogenic inactivating variant in the *SMARCB1* gene on chromosome band 22q11.2, also referred to as the *SMARCB1* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1) /INI1/ BAF47/hSNF5 locus (4,5). In 2% the *SMARCA4* gene is involved. Both genes are tumor suppressor genes and give rise to subunits of the SWI/SNF (mammalian switch/sucrose non-fermentable) or BAF (BRG1/BRM-Associated Factor) ATP-dependent chromatin-remodeling complex (4–6). This complex controls the chromatin structure and is responsible for regulating gene transcription (1,7). It facilitates DNA replication, selective gene transcription, DNA repair and recombination (8). Dysregulation of the SWI/SNF complex in cancer can result in either loss-of-function of tumor suppressors and/or gain-of-function of oncogenic mechanisms (8). Their tumor-suppressing effects are likely due to the disruption of multiple coordinated pathways, rather than a single downstream target pathway. This is because the complex interacts with a large number of proteins and active enhancers, suggesting a broader impact on lineage-specific signaling pathways (9). Inactivation of the *SMARCB1* gene is also described within other tumors, for example, schwannomas, meningiomas, myeloid sarcoma, chondrosarcoma, ganglioglioma etc. (5,6,10). Inactivation of *SMARCA4* can also cause small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) and *SMARCA4*-deficient undifferentiated thoracic tumors (1,8).

Pathogenic variants in *SMARCB1* and *SMARCA4* can be somatically acquired, but 25-35% of the patients have a germline pathogenic variant in these genes which gives rise to the rhabdoid tumor predisposition syndrome (RTPS). A germline pathogenic variant in *SMARCB1* is causing RTPS1, while RTPS2 is caused by a germline pathogenic variant in *SMARCA4* (12). From these germline pathogenic variants, the majority originate de novo, however some cases of autosomal dominant inheritance and gonadal mosaicism are described in literature (2,5). Patients with RTPS follow Knudson's two-hit hypothesis, requiring besides the germline a second hit such as a somatic pathogenic variant or loss of the wild-type allele in the tumor, to develop an RT (6,9,11,12). They usually develop tumors at a median age of 4-7 months (sometimes even in the prenatal period), compared to children with sporadic RTs with a median age of 18 months. In addition, RTPS is characterized by aggressive and often synchronous tumors at diagnosis and by metachronous tumors. All these factors contribute to a worse prognosis in patients with this germline pathogenic variant (4,6,13).

Treatment options depend on several parameters, such as the age at diagnosis, the tumor location and the presence of metastasis. The EU-RHAB protocol proposes multimodal treatment including complete chirurgical resection, chemotherapy (also intraventricular in case of ATRT) and radiotherapy (4). In 58% of the children with RTPS who developed an RT, progression during chemotherapy occurs. Thereby most children die of progressive disseminated disease (2,14). Despite intensive multimodal therapy, 5-year overall survival rates of only 17% to 36% are reported by several studies (15,16).

The goal of this review is to give an overview of published families affected by RTs due to gonadal mosaicism. Moreover, we want to raise awareness of the possible recurrence of an RT in siblings of patients with an RT that seems to be caused by a 'de novo' pathogenic variant but in reality, is an RTPS due to gonadal mosaicism, emphasizing the importance of extensive genetic testing and counseling.

Case report

A 9-mont-old presented to the emergency department with an acute abdomen. Radiographic evaluation showed a renal mass suspicious for nephroblastoma, as well as lung metastases. Preoperative chemotherapy (vincristine, actinomycin D and doxorubicin) was started according to SIOP-WT 2001 protocol (17). He had surgery with a right-sided nephrectomy, partial colectomy and para-aortic lymphadenectomy. Anatomic-pathological examination shows an MRTK local stage III because of positive lymph nodes. The postoperative chemotherapy was changed to EU-RHAB protocol (18). Nevertheless, tumor progression occurred with locoregional relapse and the development of liver metastases. Together with the parents we decided to stop chemotherapy and start palliative care. The patient died at the age of 15 months.

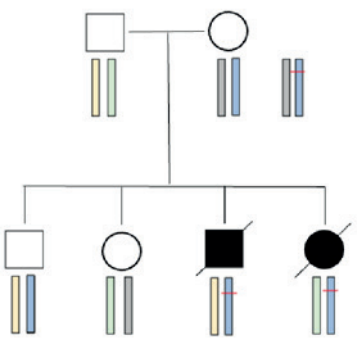
The subsequent results of the germline genetic analysis showed a heterozygote nonsense pathogenic variant NM_003073.5: c.601C>T p.(Arg201*) in the *SMARCB1* gene confirming the diagnosis of RTPS1. The parents also underwent genetic testing for this specific variant on white blood cells. This *SMARCB1* variant was absent by Sanger sequencing. It was therefore concluded to be a de novo mutation, keeping in mind that gonadal mosaicism could not be ruled out. Following the identification of the germline pathogenic variant in the boy, the parents were genetically counseled, but the mother was already pregnant at that time. At the same time, the non-affected 6-year-old brother and the 4-year-old sister of the boy were tested. The *SMARCB1* variant was absent in these two children.

A girl was born and there were no pre- and perinatal problems. At the age of 2 weeks, she presented with drinking difficulties and failure to thrive. A comprehensive diagnostic work-up showed a fossa posterior mass in the right cerebellopontine angle most compatible with ATRT based on MRI and the familial history. No biopsy was performed. Urgent germline genetic analysis in the girl confirmed the presence of the same *SMARCB1* pathogenic variant as her brother. Together with the parents it was decided to start palliative care and she died at the age of 5 weeks.

Because of two cases of malignant rhabdoid tumor in the same family with the same germline *SMARCB1* pathogenic variant, more extensive genetic analyses were performed in both parents as we were unable to detect this variant with Sanger sequencing in their white blood cells. To verify the presence of gonadal mosaicism, Sanger sequencing for the *SMARCB1* variant was negative on the spermatocytes of the father. In addition, deep next-generation sequencing for this variant (>345 000 reads) did not identify the *SMARCB1* variant. Thereafter, deep next-generation sequencing for this variant (>134 000 reads) did not identify the *SMARCB1* variant in the blood of the mother. As a next step, to evaluate whether the *SMARCB1* variant was present on the maternal allele, a haplotyping study was performed using the Human CytoSNP v1.2.-Infinium protocol. Single nucleotide polymorphism (SNP) array data from all family members were generated. The Human CytoSNP v1.2 is a streamlined panel designed for whole-genome scanning, enabling high-throughput analysis of genetic and structural variations. This panel is a product of the Infinium, which offers high sensitivity and specificity and it is particularly useful for identifying mosaicism, crucial for diagnosing genetic disorders (19,20).

To summarize the results of the mutation analysis and SNP haplotyping, a two-generation family of 6 people is presented, two parents and 4 children (Figure 1). The two younger affected children carry the same maternal allele with the *SMARCB1* pathogenic variant and a different paternal allele. The two older non-affected children carry a different maternal allele without the *SMARCB1* pathogenic variant. The non-affected son carries the same maternal allele as the 2 affected children; however, the only difference is that the pathogenic *SMARCB1* variant is not present. The non-affected children carry a different paternal allele. This haplotyping study determined that the variant is inherited from the mother, resulting from a mutation in mosaicism in the oocytes, probably occurred during oogenesis. This finding supports the suspicion of gonadal mosaicism.

Figure 1: Pedigree of the family.
The brother and sister had the same SMARBC1 variant c.601C>T p.(Arg201*). Neither parent carried the variant in their white blood cells investigated by Sanger sequencing. Haplotyping by generating SNP data of all family members showed that both children inherited the same maternal allele and a different paternal allele, which is consistent with gonadal mosaicism in the mother.



Methods

The PubMed databases were accessed from November 2021 until October 2023 for case studies, case series and reviews. The following medical subject headings (MeSH) terms were used: "rhabdoid tumor", "rhabdoid tumor predisposition syndrome", "rhabdoid tumor predisposition syndrome" AND "gonadal mosaicism, "gonadal mosaicism'. All the resulting titles were manually screened. Subsequently, an assessment of the abstracts was performed, followed by the review of the full texts as the basis for inclusion. Subsequently, the references of all retained papers were examined for relevant studies. In total 26 articles were retrieved. Informed consent was obtained from both parents to publish this case report.

Literature review and discussion

We described a new family consisting of 4 children of whom 2 siblings were diagnosed with an RT caused by a germline pathogenic variant in *SMARCB1* due to maternal gonadal mosaicism. A review of the literature only reports 7 families with RTPS due to gonadal mosaicism, as summarized in Table 1. Regarding sex, results confirm the known slight male predominance; a 1.3-1.5 male-to-female ratio, by the occurrence of a malignancy in 9 boys and 7 girls (10). In all cases the RT diagnosis was made at a very young age, with the oldest only 12 months old. Although ATRT is reported as the most prevalent type, germline pathogenic variants do not increase the chance of a certain tumor location (21). In all reported families except for one, the diagnosis of RTPS due to gonadal mosaicism was only made after a recurrence of an RT in another sibling (22). This was also the case in our family.

We will provide a discussion regarding (i) why and for whom genetic testing is crucial to perform; (ii) the possibility and difficulties to make predictions for other family members based on genetic testing; (iii) current general recommendations for clinical surveillance in RTPS.

Literature rarely reports large pedigrees with transmission of the germline pathogenic variant across generations due to the diagnosis of RT at a very young age and the often fatal outcome. Germline pathogenic variants are mostly found in patients with congenital presentation or early-onset RT, advanced stage of RT at diagnosis, synchronous RTs and a family history of RT or RTPS (6). However, the European Society of Pediatric Oncology Host Genome working group (SIOP-HGWG) strongly advises to offer all patients with an RT genetic counseling and testing for a *SMARCB1* and *SMARCA4* germline pathogenic mutation (13). In case of the presence of a germline pathogenic variant in the affected child, parents and also siblings, need to be offered genetic counseling and testing. This regardless

of the parents' results due to the possibility of gonadal mosaicism. Patients with an SCCOHT should be tested for a germline *SMARCA4* pathogenic variant and if present, first-degree relatives should also be offered genetic counseling and testing. The purpose of genetic testing and counseling in case of a pathogenetic variant is to offer the possibility of a surveillance program for family members. A surveillance program aims to detect and treat tumors in an early stage thereby possibly improving survival rates. Besides the possibility of following a surveillance program, the presence of a pathogenic variant also implies the possibility of performing prenatal genetic testing or preimplantation genetic testing (PGT) (13). The decision to undergo PGT is a complex and personal one, but given the severity of the disease, its use is justified (22–24). In general, genetic counseling and testing are important to help affected family members make informed decisions whether or not to follow a surveillance program, to perform prenatal testing or PGT.

There are multiple reasons why predicting the risk of developing an RT within siblings of families with RTPS is difficult.

First, most germline *SMARCB1* and *SMARCA4* pathogenic variants within RTPS appear de novo. Therefore, besides routine genetic testing, no other genetic tests are performed when parents don't carry the pathogenic mutation in their white blood cells, especially when it is the first child in the family with an RT. Nonetheless, recurrence in siblings of healthy parents is possible due to gonadal mosaicism and may be more common than previously believed (2,6,23). When patients and their families undergo genetic counseling for a presumed de novo mutation, they are informed about the estimated 1% recurrence risk due to gonadal mosaicism. Unfortunately, no good data on the prevalence of apparent de novo mutations due to gonadal mosaicism within RTPS are available. This, among others, because the most exact method to detect gonadal mosaicism involves direct examination of germ cells for the pathogenic mutation. Paternal gonadal mosaicism is relatively easy to detect by collecting sperm cells and examining them by routine genetic tests for the presence or absence of the pathogenic mutation. In contrast, to identify maternal gonadal mosaicism a biopsy to evaluate oocytes is necessary. This is an invasive procedure that is almost never done in clinical practice. Moreover, there are currently no molecular diagnostic tests available that are routinely performed in daily clinical practice to detect maternal gonadal mosaicism, estimating there is an ever-higher underrepresentation in the literature of maternal gonadal mosaicism. This is also reflected in the data available from the reported families with RTPS due to gonadal mosaicism (see Table 1): 4 were paternal, 1 maternal and 2 not further specified (maternal or paternal). Taken together, gonadal mosaicism may be more common than previously believed, but it is imperceptible in routine genetic testing on blood samples (2,6,23). In case gonadal mosaicism is proven, it remains challenging to estimate the risk of recurrence in siblings, as it depends on the proportion of germ cells that carry this variant which is, even more in the case of maternal gonadal mosaicism, difficult to estimate (23,24).

Secondly, when a germline pathogenic variant in *SMARCB1* is confirmed, there is a high penetrance >90% by 5 years, but this is an incomplete and estimated penetrance (13). Only some small studies are available that report a few unaffected carriers such as the study of Eaton et al. reporting 22 cases of RTPS1 of whom 7 cases had an unaffected parent that carried the pathogenic variant (5,25). The reason for this incomplete penetrance is unknown. The current high estimated penetrance in patients with RPTS1 could be influenced by selection bias emphasizing the need to perform larger studies involving systematically screened trios (parents and affected offspring) to accurately define penetrance. There is even less data on the penetrance within RTPS2, making it at the moment almost impossible at the moment to make predictions (13).

Thirdly, as outlined in cases by Bourdeaut et al., there is no clear genotype-phenotype correlation. The same germline pathogenic variant may lead to the development of different types of RT at various ages. Furthermore, distinct tumor types may differently impact family members who carry the same variant in an unpredictable manner (21). This difficulty in predicting the phenotype linked with a certain genotype is also a concern in genetic counseling. Additionally, other tumors can occur in individuals who have been successfully treated for an initial RT, as alterations in SMARBC1/*SMARCA4* are not specific to RT (26,27). With RTPS1 there is a chance of developing late-onset schwannomas and meningiomas, particularly associated with splice site and missense mutations in *SMARCB1* (2,21). Females, 5-46 years of age, with RTPS2 have a higher risk of developing SCCOHT. This tumor can be regarded as a special type of MRT, given its close clinical, histologic and (epi)genomic resemblance to RTs (12). So, the presence of a germline pathogenic *SMARCA4* variant makes it necessary to offer genetic counseling and testing for women until 45 years of age in that family (13,28).

To date, there are no official recommendations for surveillance of carriers of germline *SMARCB1* or *SMARCA4* pathogenic variants. In 2020 the SIOP-HGWG organized a panel discussion with pediatric oncologists and genetics. They drafted a proposal outlining a surveillance program targeting unaffected carriers of *SMARCB1* or *SMARCA4* pathogenic variants and long-term survivors of RT (13). Among other sources, the article of Foulkes et al. was the basis for their recommendations (12). For carriers of a

Table 1 : Clinical and molecular features of cases reported with *SMARCB1* gonadal mosaicism

Reference	Gender	Age (months)	Type of malignancy	SMARCB1 pathogenic variant NM_003073.3	Inheritance	Method to identify genetic origin of mutated allele
Sévenet *et al.* (27) (Pedigree 2)	M	3	Medulloblastoma	Unknown	Paternal mosaicism	Segregation and LOH analyses
	M	/	RT soft tissues of the neck	c.472C>T, p.(Arg158*)		
Sévenet *et al.* (27) (Pedigree 3)	M	4	Choroid plexus carcinoma	c.591del, p.(Gln198Argfs*11)	Maternal mosaicism	Segregation and LOH analyses
	F	2	ATRT	c.591del, p.(Gln198Argfs*11)		
	M	12	ATRT	c.591del, p.(Gln198Argfs*11)	Maternal mosaicism	
Lee *et al.* (28)	M	7	MRTK	c.472C>T, p.(Arg158*)	Gonadal mosaicism	/
	F	5	ATRT	c.472C>T, p.(Arg158*)	Gonadal mosaicism	
Eaton *et al.* (5)	F	5	Bladder sarcoma	c.20_43delinsT, p.(Ser7Ilefs*56)	Paternal mosaicism	Chromosome 22q microsatellite analysis
	F	2	ATRT	c.20_43delinsT, p.(Ser7Ilefs*56)	Paternal mosaicism	
Bruggers *et al.* (14)	M	0	ATRT	Unknown		Single-nucleotide polymorphism array and multiplex ligation-dependent probe amplification
	F	5	ATRT	c.(362+1)_(363-1)_(c.628+1_629-1)	Paternal mosaicism	
	M	0.5	ATRT	c.(362+1)_(363-1)_(c.628+1_629-1)	Paternal mosaicism	
Bourdeaut *et al.* (19)	M	3	ATRT	c.472C>T, p.(Arg158*)	Paternal mosaicism	/
	F	8	Spinal ATRT	c.472C>T , p.(Arg158*)	Paternal mosaicism	
Gigante *et al.* (20)	M	9	MRT and ATRT	Deletion, LOH 22q	Paternal mosaicism	Chromosome 22q microsatellite analysis
	F	prenatal	/	Deletion, LOH 22q	Paternal mosaicism	

M: Male; F: Female; RT: rhabdoid tumor; MRT, malignant rhabdoid tumor; ATRT, atypical teratoid rhabdoid tumor; MRTK, malignant rhabdoid tumor in the kidney; MRT malignant rhabdoid tumor; LOH 22q: Loss of heterozygosity of the long arm of chromosome 22

SMARCB1 or *SMARCA4* pathogenic variant who have not yet developed a tumor, clinical monitoring should be started as soon as possible. The proposed surveillance program by the SIOP-HGWG includes extensive clinical examination every 4-6 weeks and an MRI of the brain together with an ultrasound of the abdomen and kidneys every 3 months during early infancy through the age of 5 years (7,13). The likelihood of experiencing a new onset of RT significantly diminishes after 5 years of age. Nonetheless, it remains advisable to continue follow-up, not only for MRT but also for other potential manifestations such as schwannomas and meningiomas (6). Here the SIOP-HGWG proposes a physical examination every 6 months and a yearly whole-body MRI (13). But for how long can a long-term follow-up program be justified? Some case reports suggest a lifelong threat, but the risk of an RT in unaffected carrier parents is not thoroughly assessed. Thus, it is essential to properly educate patients to seek medical advice when symptoms occur so that imaging can be done in a timely manner. The SIOPS-HGWG proposes the same surveillance program for children with RTPS who were treated for an RT, on top of their own specific follow-up schedule for their treated tumor type hereby also keeping in mind the risk of secondary tumors. For all females who carry a *SMARCA4* pathogenic variant, it is recommended to continue surveillance from 5 through the age of 45 with a gynecological ultrasound due to the increased risk of SCCOHT. On a case-by-case basis, preventive oophorectomies can be discussed considering factors such as the patient's age and pregnancy wish, family history and, ideally, new studies to better estimate the risk (12,13,28). Finally, it remains unclear what to do with parents of children with RTPS due to gonadal mosaicism. To date, no studies are available reporting RT or other related tumors in parents with *SMARCB1* or *SMARCA4* gonadal mosaicism.

Conclusion

We described a family with 2 successive siblings diagnosed with RT due to a germline nonsense pathogenic variant in *SMARCB1* caused by maternal gonadal mosaicism. It is important to be aware of the possible recurrence of an RT in siblings of patients with an RT that appears to be caused by a 'de novo' pathogenic variant but is actually RTPS caused by gonadal mosaicism. Literature review only described seven other families affected by RTPS due to gonadal mosaicism. With the advent of new and more extensive genetic tests, more families with RTPS due to gonadal mosaicism will likely be identified. However, most germline *SMARCB1* and *SMARCA4* pathogenic variants in children of healthy parents arise de novo, making it challenging to predict the risk of RT development in siblings. Therefore, extensive genetic testing in families with a child affected by RTPS is crucial to rule out gonadal mosaicism and to predict more accurately the possible recurrence risk of RT within siblings.

Surveillance recommendations for carriers of *SMARCB1* or *SMARCA4* pathogenic variants are currently evolving, with proposed programs for unaffected carriers and long-term survivors of RT. However, the duration of long-term follow-up remains a topic of debate. Moreover, literature mentions nothing about the follow-up of parents of children affected by RTPS due to gonadal mosaicism. Further research and collaboration in this field are essential to provide better guidance and support to affected families.

Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript..

Acknowledgments

The authors thank the parents who shared valuable information and insight into this disease. We want to thank Cindy Melotte and Eftychia Dimitriadou for their technical assistance with SNP haplotyping.

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