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Myogenic tumors in Nevoid Basal Cell Carcinoma syndrome

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Abstract

In mice, activated Hedgehog (Hh) signaling induces tumors with myogenic differentiation. In humans, hyperactive Hh signaling due to germline *PTCH1* mutations has been linked to Nevoid Basal Cell Carcinoma syndrome (NBCCS). We report an embryonal rhabdomyosarcoma in a 16-months old girl with NBCCS and review the literature on myogenic neoplasms in NBCCS, including 8 fetal rhabdomyomas and 3 rhabdomyosarcomas. Of note, three population studies, including 255 individuals with NBCCS aged 4 months to 87 years, did not identify any myogenic tumors. Thus, myogenic tumors in NBCCS are rare and include both rhabdomyosarcomas and fetal rhabdomyomas.

Introduction

Tumors with myogenic differentiation have been reported in genetically engineered mice with activated Hedgehog (Hh) signaling [1,2] and in humans with Nevoid Basal Cell Carcinoma Syndrome (NBCCS; also known as Gorlin syndrome) [3]. NBCCS has been linked to hyperactive Hh signaling due to inactivating germline mutations in *PTCH1* [3]. We report the case of a 16-month-old girl with embryonal rhabdomyosarcoma in the left postauricular area and familial NBCCS due to a splice site mutation at intron 15

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(IVS15-1G>A) of the *PTCH1* gene. This case included, there are 4 published cases of rhabdomyosarcoma and 8 cases of fetal rhabdomyoma in individuals with NBCCS syndrome.

Case

A 16-month-old girl presented with a rapidly growing mass in the left postauricular area. The tumor was completely resected. On histologic evaluation, the tumor was focally cellular with atypical nuclei and 4 mitoses per 10 high power fields (Figure 1). 20–30% of tumor cells were positive for myogenin (myf-4). Tumor cells were positive for desmin as well. Histology and immunophenotype were diagnostic of embryonal rhabdomyosarcoma. Staging workup did not reveal any metastases. Pertinent findings on physical examination included macrocephaly and plantar pits. The patient's father had a history of NBCCS, and the patient thus met clinical criteria for NBCCS [3]. Sequencing for germline-derived *PTCH1* mutations was performed on genomic DNA extracted from peripheral blood lymphocytes obtained from the patient and her father; both were found to have splice site mutations at intron 15 (IVS15-1G>A; c.2560+1G>A) of the *PTCH1* gene. This mutation destroys the canonical splice acceptor site and is expected to result in abnormal splicing of *PTCH1*, thus confirming the clinical diagnosis of NBCCS. Of note, this mutation has not been documented as a low-frequency polymorphism in the general population as per the NHLBI Exome Sequencing Project, Exome Variant Server (EVS), but it was previously found in the genome of a chondrosarcoma [4]. The patient's final diagnosis was embryonal rhabdomyosarcoma, group I, stage I in the setting of familial NBCCS. The patient completed adjuvant chemotherapy as per Children's Oncology Group protocol ARST0331. She did not receive radiotherapy. She continues to be rhabdomyosarcoma-free 7 years after her initial diagnosis.

Discussion

NBCCS predisposes affected individuals to develop a spectrum of malignancies, most commonly basal cell carcinomas and medulloblastomas [5–7]. NBCCS also has been linked to a genetic susceptibility to develop rhabdomyosarcoma [1,8]. However, rhabdomyosarcomas in individuals with NBCCS are uncommon, as 3 NBCCS population-based studies [5–7], including a total of 255 individuals aged 4 months to 87 years with clinical NBCCS in the United States, Australia and the United Kingdom, did not identify any cases of rhabdomyosarcoma or other tumors with myogenic differentiation. In the absence of a positive family history, the clinical diagnosis of NBCCS in young children may be difficult, as many findings (e.g. maxillary cysts and basal cell carcinomas) develop with increasing age and may not be present at a young age. Yet, it is safe to conclude that rhabdomyosarcoma in the setting of NBCCS is very rare.

We queried PubMed using the search terms “rhabdomyosarcoma” and “rhabdomyoma” in conjunction with “Nevoid Basal Cell Carcinoma Syndrome”, “Naevoid Basal Cell Carcinoma Syndrome” or “Gorlin's syndrome”. This search identified 11 relevant case reports (Table 1), including 3 cases of rhabdomyosarcoma [8–10] and 8 cases of fetal rhabdomyoma [11–18]. Of note, the tumors reported by Schweisguth et al in 1968 (prior to

the first description of fetal rhabdomyomas as a tumor entity in 1972 [19]) were re-classified as multifocal fetal rhabdomyomas for the purpose of this review, because the history and histologic images provided in the report are suggestive of multifocal fetal rhabdomyoma rather than rhabdomyosarcoma [15]. All 11 patients met clinical criteria for NBCCS, and a pathogenic germline mutation in *PTCH1* was documented in one patient with fetal rhabdomyoma [16].

Fetal rhabdomyomas typically arise in children and younger adults, have a predilection to occur at head/neck sites, do not metastasize and are cured by surgical resection alone. For patients with fetal rhabdomyomas in the setting of NBCCS, histologic images were available for all 8 published cases and appeared consistent with fetal rhabdomyoma. Age at the time of tumor diagnosis was < 1 month to 36 years. Tumor sites included the head and neck (4 tumors), chest wall (3 tumors), retroperitoneum/mediastinum (3 tumors) and thigh (1 tumor). Three of 8 patients (cases 1, 6, 8) presented with multifocal fetal rhabdomyomas. These 3 patients were tumor-free 4 to 20 years after first diagnosis, but 2 of them had local recurrence of their fetal rhabdomyoma (Table 1).

Rhabdomyosarcomas are a heterogeneous group of metastasizing sarcomas with myogenic differentiation. We identified 4 patients with rhabdomyosarcoma in the setting of NBCCS. A diagnosis of embryonal rhabdomyosarcoma was verified in the patient reported here (case 12) and the patient reported by Cajaiba et al (case 10) [8]. Heney et al and Beddis et al reported embryonal rhabdomyosarcomas in 2 individuals with NBCCS, but their reports did not include any histologic images (cases 9, 11) [9,10]. Notably, three of 4 rhabdomyosarcomas in NBCCS patients originated at head and neck sites. Follow-up data were available for 2 of the 4 patients. The patient reported by Heney et al (case 11) died from disease; his tumor was located in the nasopharynx, it was not resectable and failed to respond to chemotherapy. The patient reported here (case 12) is alive and disease-free 7 years after her tumor diagnosis (Table 1).

Importantly, somatic mutations in the Hh receptor *PTCH1* were previously detected in 7 non-alveolar rhabdomyosarcomas by FISH [16,20] and in 3 out of 5 human fetal rhabdomyomas [21]. This case review includes all published cases of NBCCS-associated myogenic tumors and shows NBCCS confers susceptibility to myogenic tumor phenotypes previously linked to *PTCH1* mutations, including rhabdomyosarcomas and fetal rhabdomyomas.

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Figure 1.
Group 1, stage 1 embryonal rhabdomyosarcoma in a 16-

Table 1

Myogenic tumors in humans meeting clinical criteria [3] for Neuro Basal Cell Carcinoma Syndrome (NBCCS). Myogenic tumors in humans meeting clinical criteria for Neuro Basal Cell Carcinoma Syndrome (NBCCS). Pubmed was queried using the search terms “rhabdomyosarcoma” and “rhabdomyoma” in conjunction with “Neuro Basal Cell Carcinoma Syndrome”, “Neuro Basal Cell Carcinoma Syndrome” or “Gorlin’s syndrome”. 11 relevant case reports were identified, including 8 individuals with fetal rhabdomyoma and 3 patients with rhabdomyosarcoma.

Case	Dx	Age at 1 st Dx	Sex	Tumor number	Tumor Sites	Ptch1 (germ-line)	Distant/ regional mets	Outcome	Ref.
1	FRM	<1 months	F	2	left thigh, chest wall	n/a	None	Tumor-free 4 years after Dx	[12]
2	FRM	6 years	F	1	mediastinum/ retroperitoneum	n/a	None	n/a	[13]
3	FRM	15 years	M	1	retroperitoneum	n/a	None	n/a	[14]
4	FRM	17 years	M	1	mediastinum	n/a	None	n/a	[19]
5	FRM	<1 months	M	1	tongue	n/a	None	n/a	[18]
6	FRM	<1 months	M	3	presteral, submandibular,	n/a	None	1 local recurrence, tumor free 20 years after Dx	[15]
7	FRM	36 years	F	1	submandibular	c.1370T	None	n/a	[17]
8	FRM	< 1 months	M	2	presteral, submandibular	n/a	None	1 local recurrence, tumor-free 7 years after Dx	[16]
9	RMS	4 years	F	1	nasopharynx	n/a	None		[10]
10	RMS	5 years	M	1	bladder	n/a	None		[8]
11	RMS	8 years	M	1	nasopharynx	n/a	None	Dead of disease	[11]
12	RMS	16 months	F	1	postauricular	IVS15- 1G>A	None	Tumor-free 7 years after Dx	-