Published in final edited form as:

Ann Diagn Pathol. 2012 December ; 16(6): 504–507. doi:10.1016/j.anndiagpath.2011.04.008.

Molecularly confirmed primary malignant rhabdoid tumor of the urinary bladder: implications of accurate diagnosis

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Abstract

Malignant rhabdoid tumors (MRTs) are well recognized in the kidney and extrarenal sites such as soft tissues, retroperitoneum, and bladder but are classified as atypical teratoid/rhabdoid tumors in the central nervous system. The unifying features of both extracranial MRT and atypical teratoid/rhabdoid tumors are the exon deletions/mutations of the *SMARCB1* (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1) gene in 22q11.23 and resulting loss of SMARCB1/INI1 (integrase interactor 1) protein expression by immunohistochemistry. We herein report a case of extrarenal rhabdoid tumor confined to the bladder in a 3-year-old child, diagnosed by histopathology and confirmed by immunohistochemical and molecular studies. This is only the fourth molecularly proven primary MRT of the bladder to be reported. The patient's peripheral blood was negative for the deletions observed in the tumor, thereby confirming a sporadic origin for the tumor. Given the possible dismal outcome, urgency for definitive diagnosis to institute intensive multimodality therapy, histopathologic differential diagnosis with rhabdomyosarcoma and urothelial carcinoma with rhabdoid features, and lack of consensus management guidelines, oncologists, urologists, and pathologists must be aware of this entity. Evaluation for a germ line *SMARCB1* alteration may greatly aid risk stratification and family planning.

Keywords

Rhabdoid tumor; Pediatric; Bladder; Molecular; INI-1; ATRT

1. Introduction

Malignant rhabdoid tumors (MRTs) occurring in renal or extrarenal sites and their central nervous system (CNS) counterparts, atypical teratoid/rhabdoid tumor (AT/RT), are rare,

highly aggressive pediatric tumors. They typically arise in infants with a median reported age of 22.5 months [1,2]. The histologic diagnosis is based upon sheets of tumor cells with characteristic cytomorphology (eccentric nuclei, prominent nucleoli, eosinophilic cytoplasm with eosinophilic inclusions). The histologic diagnosis is supported by lack of immunohistochemical staining for SMARCB1/INI1/BAF47, indicating loss of protein expression [1]. Molecular studies of true rhabdoid tumors highlight exon deletions or mutations of the *SMARCB1* (*hSNF5/INI1*) tumor suppressor gene at chromosomal locus 22q11.23 [1,3-5]. This mutation/deletion results in biallelic inactivation of the gene, which correlates well with immunohistochemical loss of INI1 protein expression [1,6,7] and is a characteristic of about 98% of both extracranial MRT and AT/RT [1,3-8].

Although more commonly described in the kidney or the CNS, rhabdoid tumor has been described in a wide variety of extrarenal sites including the liver, abdomen, and retroperitoneum. Rare cases of pure rhabdoid tumors have been described in the bladder; only a handful of which have been confirmed by cytogenetic/molecular studies (Table 1) [4,9-12]. Moreover, other more commonly occurring tumors in the bladder including rhabdomyosarcoma and urothelial carcinoma can show focal rhabdoid features, thereby requiring molecular studies to confirm the diagnosis [13-15]. Herein, we report an unusual case of pure rhabdoid tumor confined to the bladder in a 3-year-old boy, which was successfully diagnosed on histopathology and confirmed by INI1 immunostaining as well as molecular studies at our referral centers.

2. Case report

A 3-year-old boy presented to our emergency department with complaints of intermittent gross hematuria first noticed the day prior. His mother had also noted decreased appetite and weight loss over the preceding month. Physical examination of the abdomen was normal. An ultrasound revealed a solid heterogeneous mass with internal vascularity extending from the anterior wall projecting into the lumen. The mass measured $2.3 \times 2.1 \times 1.5$ cm. A follow-up computed tomographic (CT) scan confirmed the presence of the mass at the dome of the bladder with no obvious extravesical extension or pelvic lymphadenopathy. Pediatric urology and oncology were consulted.

An initial cystoscopic biopsy was suspicious for malignancy but nondiagnostic due to the small size of the specimen and marked crush artifact. Therefore, a partial cystectomy was performed excising the mass at the dome of the bladder with wide surgical margins. There was no evidence of local extension outside the bladder. Received was a polypoid mass, which was nonencapsulated, soft, and fleshy on cut section without definite necrosis. Hematoxylin and eosin slides on formalin-fixed, paraffin-embedded tissue revealed a cellular neoplasm, which was somewhat well circumscribed and was submucosal in nature. The neoplastic cells were arranged in loose cords or nests and did not infiltrate deep into the muscularis propria (Figs. 1 and 2). The tumor focally reached the resection margin. In better preserved areas, the neoplastic cells were small to medium in size with eccentric nuclei with prominent nucleoli (Fig. 3). The cytoplasm was deeply eosinophilic in these cells and had a globular appearance just next to the nuclei.

A battery of immunohistochemical stains was performed. These cells were negative for pankeratin, EBV (Epstein-Barr virus), desmin, myogenin, S-100, WT1 (Wilms tumor), CD31, CD34, CD45/LCA, CD43, CD20, CD3, CD5, CD30, ALK1 (anaplastic lymphoma kinase), TdT (terminal deoxynucleotidyl transferase), MPO (myeloperoxidase), CD68, CD4, and CD8, therefore essentially ruling out a hematopoietic neoplasm or rhabdomyosarcoma. Focal positivity was seen by low-molecular weight keratin, epithelial membrane antigen (EMA), and CD99, raising the possibility of primitive neuroectodermal tumor (PNET).

However, CD99 is known to be nonspecific; and morphologically, the cells had a more rhabdoid appearance. Therefore, an extrarenal rhabdoid tumor was felt to be the most likely diagnosis. An extramural consultation was obtained, which was in agreement with the possibility of an extrarenal rhabdoid tumor; and the diagnosis was subsequently confirmed via immunohistochemical staining and molecular studies of *SMARCB1/INI1*. Specifically, deletion testing of the tumor by multiplex ligation probe amplification [4] revealed 2 overlapping deletions in chromosome 22 that included the *SMARCB1/INI1* locus. The patient's peripheral blood was also tested and was negative for the deletions, thereby confirming their somatic origin. Karyotyping of the tumor was unsuccessful due to lack of metaphase cells.

Follow-up full-body CT scan as well as positron emission topographic (PET) scan was negative for metastatic disease. The patient is receiving a 30-week course of multiagent chemotherapy, including vincristine, doxorubicin, cyclophosphamide, carboplatin, and etoposide. Local control was achieved with radiation therapy that began in week 3 of chemotherapy. He received a total dose of 4500 cGy in 25 daily fractions.

3. Discussion

Rhabdoid tumors are diagnosed histologically by recognition of sheets of tumor cells demonstrating the characteristic cytomorphology (eccentric nuclei, prominent nucleoli, eosinophilic cytoplasm with eosinophilic inclusions) [1]. Histologic diagnosis is supported by lack of immunohistochemical staining for SMARCB1/INI1, indicating loss of protein expression [1,6,7] typically due to exonic deletions or mutations resulting in biallelic inactivation of *SMARCB1 (hSNF5/INI1)* tumor suppressor gene at chromosomal locus 22q11.23 [1,3-8]. Rhabdoid tumors occurring in renal or extracranial extrarenal locations are classified as MRT, whereas those in CNS are classified as AT/RT. Inactivation of the *SMARCB1* gene and loss of the protein are a characteristic of both MRT and AT/RT. However, single-base deletions, which are the most common somatic mutations observed in CNS AT/RTs, have not been described to date in the germ line or extracranial MRT [4]. Of note, besides rhabdoid tumors, loss of expression of SMARCB1 has also been observed in epithelioid sarcoma, renal medullary carcinoma, undifferentiated pediatric sarcomas, and a subset of hepatoblastomas, albeit with fewer inactivating gene deletions or mutations [4,16-19].

Although more commonly described in the kidney or the CNS, rhabdoid tumor has been described in extrarenal sites including liver, abdomen, and retroperitoneum. In addition, rare cases of pure rhabdoid tumors have been described in the bladder; only 3 have previously been confirmed by cytogenetic/molecular studies to the best of our knowledge (Table 1) [4,9-12]. Moreover, other more commonly occurring tumors in the bladder including rhabdomyosarcoma and urothelial carcinoma can show focal rhabdoid features, thereby requiring molecular studies to confirm the diagnosis [13-15]. The present case is novel in being a pure rhabdoid tumor confined to the unusual location of bladder in a 3-year-old boy, which was successfully diagnosed on histopathology and is only the fourth reported case in the literature to the best of our knowledge that was confirmed by molecular studies [4].

These tumors have a tendency to metastasize early and carry a poor outcome regardless of the site [1]. However, interestingly, 2 reported cases of pure MRT of the bladder with long-term follow-up have had good outcomes [11,12]. Overall, however, the typical published 5-year overall survival rates based on retrospective case series range from 15% to 36% [1,11,20]. The relationship between younger age (younger than 36 months) and poorer outcomes in MRT/AT/RT, regardless of location of the primary tumor, is increasingly well established [1,9,21,22]. This may explain the good overall survival in the children who were

older than 3 years with bladder primary MRT (Table 1). However, because of the small number of primary bladder MRT, this generalization cannot be made. In extracranial MRT, younger patients more likely have multifocal or metastatic tumors at presentation, in particular CNS involvement. About 10% to 20% of patients with rhabdoid tumor have a second CNS primary, namely, AT/RT. Therefore, diagnostic workup in these tumors, especially in children younger than 3 years, must include whole body imaging and magnetic resonance imaging of the brain.

Treatment of MRT/AT/RT remains highly individualized because of the rarity of the disease and lack of controlled clinical trials. Yet, some important trends emerge from the published literature. Surgery appears to play an important role particularly for AT/RT [23] and, perhaps, for renal MRT, with the rare long-term survivors documented to have complete tumor resections [1]. Other therapy has included chemotherapy and radiation [20]. The efficacy of radiation is unknown. The optimal chemotherapy for AT/RT also remains uncertain. Chemotherapy regimens have consisted of vincristine, dactinomycin, doxorubicin, and cyclophosphamide (traditionally used in the treatment of Wilms tumor) as well as cisplatin, etoposide, ifosfamide, and carboplatin. Other patients have been treated according to PNET/medulloblastoma protocols [1]. Although responses are generally poor, recent case reports have suggested better outcomes in patients older than 3 years and with high-dose alkylator-based chemotherapy and radiotherapy [21]. Evaluation for presence of any germ line *SMARCB1* mutation, which increases the risk for rhabdoid tumor and schwannomatosis in the patient and family, should be performed to allow proper family counseling and planning of more children [4].

In conclusion, pure extrarenal rhabdoid tumors are rare and may occur as a primary in the bladder. Tumors composed predominately of rhabdoid neoplastic cells, which do not stain with typical rhabdomyosarcoma markers such as desmin or myogenin, should be evaluated for this diagnosis. Molecular studies are required to confirm the diagnosis of rhabdoid tumors, to conclusively differentiate from other tumors that may show focal rhabdoid features, to establish a follow-up protocol, and to potentially aid in family planning. Workup should include full-body CT/PET scans with emphasis on the CNS. Prognosis is historically poor but improved with intensive multimodality regimens.

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Fig. 1.
The neoplasm was located in the submucosa, without significant infiltration into muscularis propria (scanning power).

Fig. 2.
The neoplastic cells were loosely arranged in cords and nests (medium power).

Fig. 3. Medium-sized cells with large, eccentric, vesicular nuclei with prominent nucleoli and eosinophilic, globular cytoplasm predominated the neoplasm (high power).

Table 1

Findings in reported cases of MRT with bladder primary

Age/sex	Site	Size (cm)	IHC positive	IHC negative	EM	Molecular testing	Outcome	Reference no.
4 y/F	Bladder (anterior/superior wall)	5	Vimentin	SMA, desmin, myoglobin	NA	NA	Alive 9 y after diagnosis	11
4 y/F	Bladder (dome)	2.4	Vimentin, SMA, EMA	Desmin, myoglobin	Yes: rhabdoid cells	NA	Alive 2 y after diagnosis	12
6 y/F	Bladder (posterior wall)	NA	Vimentin, EMA	Desmin, myoglobin	Yes: rhabdoid cells	NA	NA	10
0 mo/NA	Bladder	NA	NA	INI1	NA	+	DOD	9
6 mo/NA	Bladder	NA	NA	INI1	NA	+	DOD	9
5 mo/F	Bladder	NA	NA	NA	NA	+	NA	4
3 y/M	Bladder (anterior wall)	2.3	LMWK, EMA, CD99	Pankeratin, EBV, desmin, myogenin, S-100, WT1, CD31, CD34, CD45/LCA, CD43, CD20, CD3, CD5, CD30, ALK1, Tdt, MPO, CD68, CD4, CD8	NA	+	Alive 6 mo after diagnosis	Current case

F indicates female; M, male; IHC, immunohistochemistry; SMA, smooth muscle actin; LMWK, low-molecular weight cytokeratin; NA, not available; DOD, died of disease.