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Neck rhabdoid tumors: Clinical features and consideration of autologous stem cell transplant

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Abstract

Extrarenal malignant rhabdoid tumors (MRT) have a poor prognosis despite aggressive therapy. Adding high-dose chemotherapy with autologous stem cell rescue (HDC-ASCR) as consolidative therapy for MRT is controversial. We describe two patients, age 13 years and 19 months, with unresectable neck MRT. After chemotherapy and radiotherapy, both underwent HDC-ASCR and remain in remission over four years later. We reviewed all published cases of neck MRT, and found poorer outcomes and more variable age of presentation and time to progression than MRT at other sites. Neck MRT may represent a higher-risk subset of MRT, and addition of HDC-ASCR merits consideration.

Keywords

Malignant rhabdoid tumor; high dose chemotherapy with autologous stem cell rescue; ATRT

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Introduction

Originally classified as a variant of Wilms tumor in 1978 [1, 2], malignant rhabdoid tumor (MRT) has been identified in numerous extrarenal sites [2–4]. It is recognized for its aggressive behavior, its presentation in children younger than two years, and its male predilection [1, 5]. The origin of MRT is obscure, although it likely arises from a pluripotent embryonic source such as neuroectoderm, due to its ability to exhibit epithelial, mesenchymal, and neural histologic characteristics [2]. The loss of the tumor suppressor gene product hSNF5/INI1, encoded by the *SMARCB1* gene, is pathognomonic for rhabdoid tumors [4].

MRT carries a poor prognosis, as it often is diagnosed at an advanced stage and has a tendency to progress during or shortly after completion of therapy [2, 6]. Recurrence more than 2 years after diagnosis is rare [4]. There are no systematic data to indicate a single best approach to first line MRT management. Aggressive upfront chemotherapy with alkylating agents has shown activity against MRT [3, 4, 6, 7]. Local control also is essential, and inability to perform complete resection of the primary tumor is associated with worse overall survival [2, 4, 6] since radiotherapy (XRT) alone may be less effective for disease control [4, 6].

We present two patients with MRT presenting in the neck, both of which were not amenable to total surgical resection, and who underwent alkylator-based chemotherapy, local XRT and high dose chemotherapy with autologous stem cell rescue (HDC-ASCR). Both patients have no evidence of active disease greater than four years from diagnosis. Based on an evaluation of the available cases of neck MRT described in the literature, they appear to present at a later age, to demonstrate an overall poorer prognosis, and to have a predilection for later relapses when compared to all sites of extrarenal MRT. These features of neck MRT motivated us to consider HDC-ASCR as consolidative therapy for our patients.

Case descriptions

Patient one is a previously healthy 13-year-old male who presented with a 10-month history of progressive left-sided neck pain. The family history was negative for cancer. Physical exam demonstrated tenderness over the posterior neck and limited range of motion at the neck due to pain. Magnetic resonance (MR) imaging revealed an anterior epidural mass extending from C2–C4 (Fig. 1A and 1B). Metastatic workup, including computed tomography (CT) of neck, chest, abdomen, and pelvis, positron emission tomography scan, and bone marrow aspiration and biopsy, was negative. A C2–C4 hemi-laminectomy and a sub-total resection of tumor were performed. Histologically, the tumor was composed of solid sheets of epithelioid cells with eccentric nuclei and eosinophilic cytoplasmic inclusions (Fig. 1C). Immunohistochemistry was positive for vimentin and cytokeratin and non-reactive for hSNF5/INI1 (Fig. 1D), a loss of normal nuclear expression indicative of MRT. Genetic testing for loss of *SMARCB1* was recommended but not performed per family's preference. Differential consideration was given to epithelioid sarcoma since the two diagnoses have overlapping pathologic and molecular genetic features; however they are distinctively different in terms of age at presentation (median age for epithelioid sarcoma 26 years) and

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sites of predilection (proximal extremities for epithelioid sarcoma and kidney, truncal soft tissues, and central nervous system for rhabdoid tumors) and two independent pathology evaluations concluded the diagnosis of MRT based on current literature [8]. The patient subsequently was started on an alkylator-based, multi-agent chemotherapy regimen, modified from therapy for atypical teratoid rhabdoid tumor (ATRT) described by Chi and colleagues [9]. Chemotherapy was given over 35 weeks, consisting of vincristine, cisplatin, doxorubicin, cyclophosphamide, etoposide, and dactinomycin. Temozolomide was added in the latter half of therapy for maintenance. During weeks 7–12, he received involved-field conformal XRT consisting of 50 Gray (Gy) to the tumor bed and 40 Gy to the cervical spine. Following 35 weeks of chemotherapy, the patient's treatment was consolidated with HDC-ASCR utilizing a carboplatin, etoposide, and melphalan (CEM) conditioning regimen. The patient is now more than seven years from diagnosis with no evidence of recurrence of MRT (Fig 1E and 1F).

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Patient two is a previously healthy female, who presented at 19 months of age with progressive neck pain, torticollis, poor appetite, and fatigue over the prior several months. The family history was negative for cancer. Physical exam was remarkable for left torticollis and neck extension limited by pain. A CT scan of the head and neck demonstrated a soft tissue mass at the right skull base. Subsequent MR imaging revealed a right-sided epidural soft tissue mass extending into the suboccipital soft tissues and penetrating between C1–C2 (Fig. 2A and 2B). Metastatic workup including MR total spine, CT chest, abdomen, and pelvis, and bone marrow aspiration and biopsy, was negative. The tumor was judged unresectable and the patient underwent excisional biopsy. Pathology revealed tumor cells with eosinophilic cytoplasm and occasional rhabdoid inclusions, on a background of inflammatory cells, and occasional evidence of focal tumor necrosis (Fig. 2C). Immunohistochemistry was positive for cytokeratin and non-reactive for hSNF5/INI1 (Fig. 2D), indicative of MRT. Genetic testing for loss of *SMARCB1* in the patient and her parents was recommended but not performed. The patient subsequently was started on alkylator-based chemotherapy using revised regimen UH-1 per Children's Oncology Group (COG) protocol AREN0321 (high risk renal tumors), a modification of previous high-risk renal tumor chemotherapy from the Fifth National Wilms Tumor study [10]. Therapy was given over 30 weeks, utilizing vincristine, doxorubicin, cyclophosphamide, carboplatin and etoposide. During weeks 7–12 (at age 21–22 months), she received localized XRT delivering 50.4 Gy to the tumor bed while limiting the spinal cord to 45 Gy. Following 30 weeks of chemotherapy, the patient's treatment was consolidated with HDC-ASCR utilizing CEM conditioning. Two years after diagnosis, the patient had stable residual enhancement on MR imaging (Fig 2E and 2F), presumed to be nonviable tissue. She is now more than four years from diagnosis with no evidence of active disease. Currently six years old, she has sequelae of XRT including focal alopecia, hypothyroidism, Eustachian tube dysfunction, and neck muscle tightness; she also has mild transfusional iron overload (ferritin 340 ng/mL) that is resolving. She has not been found to have neurocognitive difficulties, ototoxicity, or dental problems.

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Discussion

The estimated overall incidence of extrarenal MRT is 0.15–0.6 per million children [3]; the incidence of MRT in the neck has not been reported. The two cases described here were the only two extrarenal MRT cases at our institution over a ten-year period. In order to better understand other centers' experience with MRT of the neck, we queried the available literature for case series of extrarenal MRT, and for case reports of MRT presenting in the neck. Table 1 lists the identified cases and case series and includes the two cases described here. A total of 16 previously-reported cases of neck MRT were identified in this analysis, and 112 cases of extrarenal MRT were described collectively in the published case series, suggesting MRT in the neck has a frequency of approximately 14% among published case series of extrarenal MRT.

This site of disease presents an added challenge of being likely unamenable to complete surgical resection. Of the published cases of neck MRT we identified, only one described initial gross total resection [11]. This feature may contribute to the collectively poor outcomes for these patients described in the available literature, as quality of local control has been found to correlate with better outcomes [12].

The age at diagnosis of neck MRT ranged from one month to 23 years; the mean and median age of the 16 patients with reported ages at diagnosis was 5.7 and 2.5 years respectively, older than the overall mean and median age at diagnosis of 1.4 and 0.9 years reported for MRT at all sites [1]. Several studies have indicated a survival advantage – with overall survival up to 38% -- for patients who present with MRT at ages older than 24–36 months [4, 12], and this correlates with data in renal MRT suggesting that those tumors occurring in older children and adolescents have a more favorable outcome [13]. However, among reported cases of neck MRT, six of seven patients diagnosed over age 36 months died of their disease (Table 1). For these individuals, age did not appear to confer a substantial advantage to overall survival.

MRT is also known to be a rapidly progressive disease, with median time to progression of 2 months in spite of therapy in one case series [4]. Within the historical cases of neck MRT that we evaluated, ten of the patients were described as dying from their disease, with eight deaths occurring between two and eight months after diagnosis; however, two of the patients progressed/relapsed 27 and 44 months after diagnosis, well after the expected timeframe for progression in MRT. These findings suggest that progression/recurrence risk for children with neck MRT may occur later than is typically seen in other MRT patients. Similarly, a previous case series of extrarenal MRT reported that four of 13 patients progressed more than 12 months after diagnosis [2].

The optimal chemotherapeutic regimen for management of MRT remains elusive, likely due to the rarity of the condition and lack of focused, prospective studies. Among patients with neck MRT, ten different chemotherapeutic regimens have been reported (Table 1), making direct comparisons challenging [12]. Most approaches included agents active against many different solid tumors, such as vincristine, cyclophosphamide, doxorubicin, etoposide, and platinum compounds [7], which we also utilized in treating our two patients.

Addition of HDC-ASCR to primary therapy for extracranial MRT has been controversial. Autologous stem cell transplant is standard of care for ATRT according to COG protocols, and has been employed in renal MRT in some cases [14]. However, there may be selection bias in the reports of successful use of HDC-ASCR in extrarenal MRT because these patients may already be good responders to chemotherapy, and the addition of the transplant may not be contributing to their better outcomes [12]. Nevertheless, the authors of one recent large case series have suggested that this modality be considered in patients who are good responders to upfront therapy [7]. A small number of patients with neck MRT have been treated with HDC-ASCR. Three patients, including the two we describe in this report, received this as part of the planned primary therapy [4, 7], and have survived 8.5, 4, and 7 years from diagnosis. One patient received HDC-ASCR as salvage therapy at time of progression (27 months), and ultimately succumbed to his disease [11]. Recognizing that the literature suggests patients with neck MRT are at risk for late relapse, have unresectable disease, and appear to have a worse overall prognosis than other sites of MRT, this therapeutic option for these patients merits further prospective study.

There are several limitations to our review of cases of neck MRT. Because of the rarity of extrarenal MRT, with neck MRT representing a small percentage of the total, there is a paucity of cases to consider, and these are likely subject to significant variability in clinical features. There may also be a publication bias regarding which patients are described in the literature, so the published cases may not accurately represent the typical clinical features of patients with neck MRT. Further, patients diagnosed with MRT in publications prior to the 1990s may be more likely to have been diagnosed by histopathology than by immunohistochemistry for hSNF5/INI1. We attempted to address this latter concern by considering only cases published since 1991 [15]. Finally, the neck represents multiple anatomic sites and is therefore a heterogeneous term for describing the location of MRT. However, as many authors who have published cases of MRT use the term “neck” to group these anatomic sites, a more precise description of the historical locations of the tumor in the neck is not possible in retrospect.

Despite these caveats, it appears that there is considerably more variability in age at diagnosis and time to relapse, as well as poorer outcomes for patients with neck MRT compared to all extrarenal MRT. Thus, the neck appears to be a particularly high-risk site of MRT. This may be due to poor primary tumor resectability or an as-yet unidentified biological difference in patients with this site of disease. Here we have reported two patients with neck MRT who have no evidence of disease at seven and four years from diagnosis, following aggressive multimodal alkylator-based chemotherapy, local control with XRT, and consolidative HDC-ASCR using CEM conditioning. The addition of upfront HDC-ASCR for these challenging patients merits further consideration and prospective study.

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Figure 1. Radiographic and histologic imaging of Patient 1

A–B, T1-weighted post contrast MR images at time of diagnosis. **A**, Sagittal imaging reveals a contrast-enhancing, extradural mass within the anterior epidural space of the cervical spine extending from C2–C4 (white arrowheads). **B**, Axial view at C2–C3 level exhibits the mass extending anteriorly through the left C2–C3 neural foramen with resultant widening of the foramen (white arrowheads). The mass partially encases the left vertebral artery (black arrowhead). **C**, Histologic image of the tumor at 600x magnification, stained with hematoxylin and eosin, after partial resection illustrates a tumor composed of uniform, malignant round cells. Some tumor cells exhibit a prominent eosinophilic or rhabdoid inclusion (black arrowheads). **D**, INI1/BAF47 immunostaining of the tumor at 600x magnification shows that the nuclei of the tumor cells are non-reactive (black arrowheads). Surrounding lymphocytes and histiocytes show intense nuclear positivity to indicate the presence of the INI1 gene and serve as internal positive controls (white arrowheads). **E–F**, MR images 3 years after diagnosis. Sagittal (**E**) and axial (**F**) T1-weighted post contrast images of the cervical spine demonstrate no evidence of residual tumor.

Figure 2. Radiographic and histologic imaging of Patient 2

A–B, T1-weighted post contrast MR images at time of diagnosis. **A**, Axial imaging at the level of the skull base reveals a ventral extradural soft tissue mass (black arrowhead), with tumor extending along the right lateral aspect of the suboccipital soft tissues (white arrowheads). **B**, Coronal view redemonstrates the mass (white arrowhead), and exhibits tumor insinuating in between C1 and C2 (black arrowhead). **C**, Histologic image of the tumor at 400x magnification, stained with hematoxylin and eosin, after biopsy illustrates tumor cells with an epithelioid or histiocytoid appearance, with abundant eosinophilic cytoplasm and occasional rhabdoid inclusions (black arrowheads), on a background of inflammatory cells consisting of neutrophils, lymphocytes and macrophages. **D**, INI1 immunostaining of the tumor at 400x magnification shows that the nuclei of the tumor cells are non-reactive (black arrowheads). Surrounding lymphocytes and capillary endothelium show nuclear positivity (white arrowheads). **E–F**, MR images 2 years after diagnosis. Coronal (**E**) and sagittal (**F**) T1-weighted post contrast images show improvement in the suboccipital component of the tumor, with minimal residual abnormal enhancement (white arrowheads) that has remained stable on serial imaging thereafter (not shown).

Table 1

Characteristics of reported extrarenal malignant rhabdoid tumors of the neck

Author	Total # extrarenal MRT	Neck MRT Cases							Outcome (time post-Dx, mo)
		#	Age at Dx (mo)	Resection	Chemotherapy	XRT (Gy)	HDC-ASCR		
Kodet, 1991 ^[15]	26	3	17 10 95	Incomplete Incomplete Incomplete	IRS IRS IRS	+ No +	No No No	Alive (45) DOD (6) DOD (4)	
Gururangan, 1993 ^[2]	13	0							
Rosenberg, 1994 ^[16]	NS*	1	30	Incomplete	Cy, E	No	No	PD, DOD (2)	
Fanburg-Smith, 1998 ^[17]	18	2	10 276	NS	NS	NS	NS	NS	
Kazan, 2007 ^[18]	NS*	1	48	Incomplete	None, declined	No	No	DOD (6)	
Madigan, 2007 ^[4] ; updated in Venkatramani, 2014 ^[7]	11	2	30 54	Delayed, total None	V, A, C, If, D V, D, C, If, E	45 19.5	Yes No	Alive (102) PD (2), DOD (5)	
Robbens, 2007 ^[5]	NS*	1	228	Incomplete	NS	No	No	PD, DOD (8)	
Bourdeaut, 2008 ^[6]	26	1	77	Delayed, incomplete	Cy, D, V, Ca, E	No	No	PD (44), DOD	
Fridley, 2009 ^[19]	NS*	1	13	Incomplete	V, D, Cy, If, Ca, E	No	No	PD (4), DOD	
Garcés-Inigo, 2009 ^[20]	9	1	1	NS	NS	NS	NS	Alive (12)	
Heuer, 2010 ^[11]	NS*	1	84	Total	V, D, Cy, P, E, A, T, ITT	54	Yes (at relapse)	PD (27), DOD (42)	
Morgenstern, 2010 ^[12]	9	1	NS	NS	NS	NS	NS	NS	
Howman-Giles, 2012 ^[21]	2*	1	20	None	V, D, Cy, Ca, E, Ir	NS	Planned	PD, DOD (6)	
Current report	2	2	156 19	Incomplete None	V, P, D, Cy, E, A, T V, D, Cy, Ca, E	50 50.4	Yes Yes	Alive (87) Alive (56)	

* These case reports were not included in the estimate of frequency of neck rhabdoid tumors described in the text.

Abbreviations: A, dactinomycin; Ca, carboplatin; Cy, cyclophosphamide; D, doxorubicin; DOD, died of disease; Dx, diagnosis; E, etoposide; Gy, gray; HDC-ASCR, high dose chemotherapy with autologous stem cell rescue; If, ifosfamide; Ir, irinotecan; IRS, based on Intergroup Rhabdomyosarcoma Study protocols (not specified); ITT, triple intrathecal therapy of methotrexate, cytarabine, hydrocortisone; mo, months; MRT, malignant rhabdoid tumor; NS, not specified; P, cisplatin; PD, progressive disease; T, temozolomide; V, vincristine; XRT, radiation therapy